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INTERNATIONAL SYMPOSIUM OF THE DEBORAH SANATORIUM AND HOSPITAL

PHILADELPHIA, PENNSYLVANIA
NOVEMBER 20–22, 1958

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FOREWORD

Under the leadership of Dora Moness Shapiro and her husband, Solomon, a group of New York volunteers founded the Deborah Sanatorium during 1922. A private hospital maintained by Dr. Marcus W. Newcomb at Browns Mills, New Jersey, was purchased and named for the prophetess Deborah, who inspired the Israelites to unity and victory over their oppressors.

When the Deborah Sanatorium was opened for patients during 1923, it consisted of four frame buildings with beds for thirty-two tuberculous patients. Although a modern fireproof building was projected in 1931, due to the depression of those days, the first two floors were not in use until 1936. The present five-story main building, including an operating room, was completed in 1948. A one-story pavilion was completed and dedicated to the care of chronic tuberculous patients in 1950. Since 1954, this building has been used for the care of cardiac patients. While the hospital buildings themselves have been growing to accommodate 166 patients, auxiliary buildings have been constructed to house the staff and hospital services.

When the Deborah Sanatorium was opened for tuberculous patients, treatment consisted predominantly of bed rest and pneumothorax, thoracoplasties being performed elsewhere as indicated. During 1954, a decision was made to open Deborah for cardiac patients. Deborah became the Deborah Sanatorium and Hospital, and more recently, the Deborah Hospital, for the treatment of pulmonary and cardiac diseases, primarily those amenable to surgical methods of treatment. Equipment and personnel are available for complete studies of respiratory and cardiac diseases. To facilitate the expanding surgery programs, a wing is being planned to accommodate operating and recovery room facilities of the most modern type.

The official motto of Deborah is: "HE WHO SERVES HUMANITY SERVES GOD: HE WHO SERVES DEBORAH SERVES BOTH." The only criterion for admission to Deborah is the need of the medical service available in the hospital. Patients have sought Deborah's care, coming from many states and from overseas. The main support of the hospital is derived through the efforts of women volunteer members of some 165 chapters located along the East Coast from Connecticut to Florida, and is supplemented by financial aid from the professions, industry, labor, and private benefactors. The Deborah Hospital relies entirely upon voluntary support and receives no governmental aid.

The International Symposium on Tuberculosis was conceived and developed to bring Deborah into the field of medical education. Tuberculosis was chosen as the topic of the first symposium, since tuberculosis had been the first medical interest of Deborah. The Symposium was organized to afford a carefully selected group of laboratory, medical, surgical, and public health specialists in tuberculosis to discuss major problems before an interested audience. In order that the proceedings of the Symposium should attain the widest circulation and usefulness, their publication was proposed early. The complete transcript of the Symposium was accepted for publication by THE AMERICAN REVIEW OF RESPIRATORY DISEASES, and Deborah was able to underwrite the costs involved in publishing the proceedings as a supplement to this journal.

The work of Deborah will continue to progress in its chosen fields of patient care and education. Other symposia are planned to encompass other areas of pulmonary and cardiac diseases.

July 15, 1959

GEORGE N. J. SOMMER, JR.
Trenton, New Jersey

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PANEL ONE

CHEMOPROPHYLAXIS OF TUBERCULOSIS

Chairman: WALSH MCDERMOTT
Introducer: SIDNEY RAFFEL
Panelists: GEORGES CANETTI
JOHANNES HOLM
EDITH M. LINCOLN
LEON H. SCHMIDT
GUY P. YOUMANS

Dr. McDermott introduced the members of the panel:

Dr. Edith Lincoln, Adjunct Professor of Pediatrics at New York University and Director Emeritus of the Children's Tuberculosis Service at Bellevue Hospital, New York, New York.

Dr. Sidney Raffel, Professor and head of the Department of Medical Microbiology at Stanford Medical College, Stanford, California.

Dr. Johannes Holm, a former laboratory investigator in the State Serum Institute in Copenhagen, and for the past decade the Director of the Tuberculosis Section of the World Health Organization, one of the most important activities of the World Health Organization today.

Dr. Georges Canetti of the Institut Pasteur of Paris. Dr. Canetti is one of those rare individuals who is both a pathologist and a microbiologist in the one person. He is Chief of Laboratories of Tuberculosis at the Institut Pasteur.

Dr. Guy Youmans, Professor and head of the Department of Microbiology at Northwestern University Medical College, Chicago, Illinois.

Dr. Leon H. Schmidt, Professor of Pharmacology at the University of Cincinnati and the Director of The Christ Hospital Institute of Medical Research in Cincinnati, Ohio.

The Chairman, Dr. Walsh McDermott, is Livingston Farrand Professor of Public Health and Preventive Medicine and Chairman of the Department, New York Hospital-Cornell Medical Center; and Editor of THE AMERICAN REVIEW OF RESPIRATORY DISEASES.

DR. MCDERMOTT: As you know, the proceedings today—and indeed during the succeeding days—will all be in the form of panels. Each panel will presumably reflect the particular prejudices of the moderator and the more forceful members of the group. We have, in effect, a nuclear panel here on the platform and an extended panel in the first two rows. Efforts will be made to include both together, but not necessarily, we hope, simultaneously.

I happen to belong to the *al fresco* school of panelists in which my great desire and instructions usually are that the people come armed with no preparation but with violent opinions. In a sense, then, you could say that this is a completely unprepared panel. In another sense, you could say that the members of the panel have been preparing for this very moment by virtue of their entire professional lives.

Our procedure will be to start with a presentation of the situation by one person and a series of colloquies from then on. The subject is chemoprophylaxis of tuberculosis. Dr. Raffel will make the opening presentation.

DR. RAFFEL: This is an unrehearsed program in the sense that there has been no collusion among us, but I can assure you that I think we have all thought intensively about what we want to say. I think the function of an introducer is often of somewhat dubious value, aside from trying to appear presentable, thus making the panel of which he is a member respectable. I think it is sometimes of dubious value because it is very easy to create a state of confusion about the subject under discussion from which the rest of the panel then tries to extricate the audience as well as the introducer during the rest of the session; and it may well be that this is what I will be doing here in the next few minutes.

However, I did think in deliberating about what should be said for a panel of this kind that some attempt should be made to introduce the pros and cons of the subject under discussion, chemotherapeutic prophylactic measures for tuberculosis, and I will attempt to do this in a once-over-lightly fashion, as it were, leaving, of course, for the panel the elaboration of the details and, I trust, the extrication from this morass that may be created.

First of all, I took this title to mean prophylaxis, prevention of tuberculosis, rather than the early chemotherapy of tuberculosis; that is, chemotherapy after tuberculin reactivity has been established. I think there is some tendency to

confuse these two issues, and I believe that without splitting hairs these should not be confused.

The latter issue, the early chemotherapy of tuberculosis, invokes certain questions which aren't present when an attempt is being made to actually prevent the disease right from the beginning. In the case of early chemotherapy, there is a situation in which the subject has already responded to the tubercle bacillus with whatever immune processes he can get together and, consequently, as I say, I think the situation has been changed.

I am going to deal, for the present few minutes at least, with the more or less pure situation of the use of drugs for the prevention of this disease. When we approach this from the philosophic standpoint, it certainly would appear to be a reasonable kind of procedure to use, say, a pinch of a disinfecting agent to season an individual so that he is distasteful to the particular agent in question, the tubercle bacillus. There are analogies for this certainly in other situations.

In the case of the Streptococcus nobody would argue the fact that penicillin, or some other appropriate antimicrobial agent, in persons with rheumatic fever is not only a desirable, but an absolutely necessary procedure to prevent further streptococcal infection.

Superficially, in the case of the tubercle bacillus and the drug, isoniazid, which is generally used or considered for prophylactic purposes, the same considerations would seem to be pertinent. We have, first of all, a drug which is relatively nontoxic, which is taken easily by mouth, and which can be taken for long periods of time. From the bacillary standpoint we have an organism which—in the test tube at least—can be killed by this drug, so that no particular questions really would seem to come up.

However, when the subject is looked at more closely on the basis of experimental work that has been done, and of certain human observations of which there have been relatively few so far, there are some obstacles to accepting this kind of approach without any question. Accordingly, I have lined up several points here simply for mention: on the one hand, that is, on the "con" side: What are the possible hindrances to the use of isoniazid as a preventive measure in tuberculosis? On the other hand: What are the "pros" of the situation? Why should this perhaps be done?

Among the cons are the following: First of all, it has been shown experimentally that infections with tubercle bacilli can be acquired by animals during the time when they are being covered by drug administration. The drug certainly doesn't set up a protective wall which prevents infection, and these organisms may remain present in the tissues, in what we might call latent form, during long periods of administration of the drug. Dr. Schmidt, a member of our panel, has done work which is especially pertinent to this point.

The second point is that, after cessation of the treatment, after the drug is no longer being given, these surviving bacilli can set up active infection. This also has been shown to be true experimentally; not in all experiments, but in a number of them.

The third and last point on the con side is the fact that animals which acquire infection while they are receiving a drug are apt not to develop immunity to the infectious agents. Thus, after cessation of treatment in cases in which the organisms have remained latently active, the host is essentially a fresh one as far as the bacilli are concerned.

This situation also has analogues. I think perhaps the best one available is that shown by Smadel in studies carried out several years ago in persons deliberately infected with the rickettsia of scrub typhus and treated with chloramphenicol at various times (either at the time of infection or at various intervals thereafter); it was shown that the earlier the treatment was started, the greater the danger of subsequent relapse.

If the organism is really suppressed—but unfortunately not entirely killed off by early administration of a drug—or if the infection occurs while the drug is actually being given, then the organisms are suppressed to a point where they never constitute a sufficient immunizing stimulus. Consequently, the patient does not become immune (and this, as I say, seems to be the case), at least so far as the majority of experimental tests have gone in tuberculosis, to infection with the tubercle bacillus which occurs while drugs are being given.

Those are the cons. As I said, others may be revealed during the course of the discussion.

The pros in the situation seem to me to be the following: the items which favor the use of the drug for purely prophylactic purposes in human beings, also three in number: First of all, as I

mentioned before, the currently useful drug for this purpose, isoniazid, is relatively nontoxic, can be used for long periods of time, and can be used conveniently; and, furthermore, it has a high level of bactericidal activity *in vitro*.

Second, the long-continued use of isoniazid does not lead to disturbances of the normal microbial flora. As you well know, this sort of thing can happen with the tetracyclines and other drugs. In the process of making the situation favorable with respect to an organism in which you are interested, unfortunately, sometimes the situation is made very unfavorable as far as other microbes in the environment, in the intestinal tract, or on the skin are concerned. This, so far as I am able to determine, does not occur with isoniazid.

The third point is that in experimental animals at least (and so far as I know the only pertinent evidence is from experimental animals), for some mysterious reason (it is certainly mysterious to me), long-continued use of the drug in the situations that I have been talking about, that is, while the animal has acquired an infection, does not result in the emergence of resistance of the tubercle bacilli to the drug in use.

I can't quite see why this should be, but all of a number of articles and reports that have been devoted to this subject have been unanimous in finding that these latent organisms which persist throughout the period of drug administration after cessation of the treatment are still actively susceptible to isoniazid. This I consider to be a point in favor of the prophylactic use of the drug because it eliminates, I hope, the possibility that by the wide use of isoniazid for prophylaxis we might eventually create a situation for the tubercle bacillus such as we have now for the Streptococcus: a large number of drug-resistant strains circulating in the population, strains for which the presently available better antimicrobial agents might not be effective.

From this morass of points, three on both sides of the question, I think perhaps two items of interest may emerge. First of all, I personally am inclined—on the basis of what I have just told you—to believe that the net epidemiologic result, the net statistical result of the use of isoniazid for the prevention of tuberculosis, should be a favorable one. True, a certain number of people (we have no way of knowing how many) who receive the drug in this way may later retain the bacilli, but the net result should be complete suppression of the organism in a sufficient number of such persons so that fewer would develop tuberculosis than would have developed it if no drug prophylaxis had been given.

Consequently, I think that on this basis alone it seems reasonable to use the drug as prophylaxis. I would like to modify that point only in one sense. Since these people (if our experimental work means anything, and I think it does), when they are deprived of the drug, will not have any immunity to the bacilli which now lie latent in their tissues, they face the organisms now as a fresh situation. It seems to me that perhaps simultaneously with the drug they should be given the benefits of having their own immunologic resources to fall back upon in addition to the drug which they have been receiving. So, it would seem to me logical, in those cases in which it is thought that prophylaxis with drug is desirable, that the subject also should be given the benefits of immunization. The benefits of immunization, then, should be derived from a strain, a vaccinating strain of BCG, an attenuated organism, which is isoniazid resistant itself (as you all know, there are such strains available) and which could persist in the tissues during the time when the individual is receiving his drug to immunize simultaneously with the suppression of the infecting bacilli.

We might thus get the double effect which, again, Dr. Schmidt has shown so nicely in monkeys, of having a disinfecting action (we might say) along with an antibacterial action dependent upon the host's own resources, which together may give us an even better net result in a group of subjects than could be obtained by the use of drug alone as a prophylactic measure.

These points, I think, bring up a number of questions and along with the rest of you I look forward to what our experts here will have to say about them. Thank you.

DR. MCDERMOTT: Thank you, Dr. Raffel.

We have heard a beautifully concise presentation of the situation by an expert. Dr. Raffel was confining his remarks to a particular area of chemoprophylaxis. Dr. Youmans and I have held forth at one time or another on how this word was being misused. We then individually made the mistake of going to the dictionary to see what it meant, and, in some seven medical dictionaries, I discovered (and I think Dr. Youmans will back me up) that the word means the prevention

of a disease or its manifestations, so it is obvious that we have problems here in terminology.

For this morning I thought it might be helpful to suggest the use of two phrases: primary prophylaxis and secondary prophylaxis. Dr. Raffel, you were talking about primary prophylaxis, namely, a situation in which the patient has no tubercle bacilli in him at all, but is exposed to tubercle bacilli. That is primary prophylaxis.

Secondary prophylaxis is the prevention of "its manifestations" after infection has taken place, namely, the use of isoniazid in somebody who is a tuberculin reactor.

With respect to primary prophylaxis, which is the obviously logical place to start, there are, crudely, two situations in clinical practice in which this might be used: one would be the child or the close associate of the person who is heavily infectious with tubercle bacilli—the as yet uninfected person who is a close associate. The other would be the rare situation of laboratory accidents in which somebody sticks his finger with a needle that has just been immersed in a lot of tubercle bacilli.

Dr. Raffel, you believe that, on balance, the use of primary prophylaxis makes sense, is that correct?

DR. RAFFEL: Yes.

DR. MCDERMOTT: It makes sense in situations of high risk?

DR. RAFFEL: I would think so, from all the evidence available.

DR. MCDERMOTT: Do you believe that the isoniazid-resistant BCG will be as good a BCG as the wild type of BCG, so to speak?

DR. RAFFEL: From the evidence I have seen, yes. I have never worked with the organism myself; some of our panelists here have. Apparently this strain immunizes as well as the wild type.

DR. MCDERMOTT: So that you would favor the use of isoniazid in the as yet uninfected close associates of the person excreting large numbers of tubercle bacilli?

DR. RAFFEL: Yes.

DR. MCDERMOTT: You have, of course, pointed out three possible disadvantages of this procedure, and one is the possibility that one could be treating too early. In the Smadel experience, in effect what they did was to treat scrub typhus too early.

DR. RAFFEL: Yes, the point being, of course, that the function of the infecting agent as an immunizing substance is thereby lost; almost complete, but not sufficiently complete, suppression has occurred.

DR. MCDERMOTT: You make the point also, I gather, that sooner or later the infected person will have to face up to having the infection.

DR. RAFFEL: A certain percentage of them will.

DR. MCDERMOTT: A certain percentage will eventually have to face up, so that what you would do in this situation is to create a solid armistice between the tubercle bacillus and the drug, and so long as you maintain the drug the armistice is enforced. Once you stop the drug, the possibility of an outbreak of hostilities is there.

DR. RAFFEL: Yes.

DR. MCDERMOTT: Dr. Lincoln, we have always heard that it is a lot worse to have a tuberculous infection at the age of six months than at the age of three years. If you could create this armistice from three months to three years, or six months to three years, and then say to the child, "Go it alone now, boy, you have to face up to it," is that child at three years as well able to face up to the infection as any other three-year-old child, or is he like a six-month-old child?

DR. LINCOLN: I don't know the answer to that, but I wouldn't trust the tubercle bacillus so far that I would want to leave a three-year-old child with tubercle bacilli and no further protection. I would be afraid he might act as some of Dr. Schmidt's monkeys and develop disease; and we know that, while the risk is a little less, possibly, there is still a considerable risk.

I would think it would be better to give isoniazid long enough after the initial exposure, say to the mother right after birth, to be sure that the child does not develop a primary infection, and then vaccinate him, not necessarily even with the isoniazid-resistant bacilli, but, granted that he is now separated from his mother, vaccinate him with ordinary BCG.

DR. MCDERMOTT: Let us take a child born of a tuberculous mother in the infectious stage, and this is discovered along about the fourth month of the child's life. The child is then put on isoniazid and separated from the mother. The child was tuberculin negative at the time this was done. The child is now treated until he is three years old, you see, treated for a two-and-a-half-year period. Now, would you be willing to stop therapy at that point?

DR. LINCOLN: I wouldn't have treated him in the beginning for two and a half years.

DR. MCDERMOTT: What would have been your procedure?

DR. LINCOLN: That was what I was trying to explain originally. I would treat him long enough to be sure that he was past the incubation period of his tuberculosis; in other words, to cover the period in which he might have become infected in spite of the late administration of isoniazid.

DR. MCDERMOTT: How long would that be?

DR. LINCOLN: We know that with therapy (certainly it has been shown with streptomycin) the incubation period is lengthened, so I suppose one would treat him for maybe two months.

DR. MCDERMOTT: Your point is that in a baby exposed but not necessarily infected (you just don't know which is the case)—that two months' treatment in that situation should bring you beyond the period of risk of the appearance of the disease.

DR. LINCOLN: No, I think it would simply cover the period in which he might have already been infected and developed the disease.

DR. MCDERMOTT: And since you then separated the child —

DR. LINCOLN: Since you have already separated the child, you will then vaccinate him against future exposure to the mother.

DR. MCDERMOTT: Dr. Schmidt, how do you feel about that?

DR. SCHMIDT: I have no experience in a clinical situation. I do feel that the interpretations which were put on the original observations which were made in our laboratory and which have been quoted widely by other people, including some of the panelists here this morning, ought to be further evaluated by the group here in the light of new work which has been done in our establishment in the two-year period since these observations were published.

You will recall that in the particular situation which we had, in which we exposed nonimmune treated monkeys to highly infected monkeys for a period of a year and then took them off treatment on the same day on which we removed the animals from contact with the infected animals, we obtained an approximately 50 per cent infection rate within a period of six months in those animals that had received isoniazid prophylaxis.

We have done two very sizable experiments since then, Dr. McDermott, which show that, if a comparatively small dose of isoniazid is given on the day of infection and daily or twice daily for a period of sixteen or twenty-four weeks thereafter, and then these animals are followed for a period of a year, essentially 100 per cent protection is found.

This, I think, indicates that one can achieve in an exquisitely susceptible test object, inoculated by the intratracheal route, essential sterilization of the tissue. Now, I know that this may be a word, sterilization, which you do not like to use and perhaps we ought to wait for another five years to find out whether the disease in these animals will break through. But these are nonimmune animals by all criteria that we can establish at the time that they are sacrificed one year after the completion of prophylaxis. It would be anticipated that such animals would develop overwhelming disease within a period of four months if they had from one to 10 tubercle bacilli in the chest cavity.

DR. MCDERMOTT: Their tuberculin reactions would remain negative too?

DR. SCHMIDT: Negative, yes.

DR. MCDERMOTT: So that your point is that, if one were fortunate enough to start isoniazid therapy at the moment of infection in a highly susceptible animal and continue that therapy for only a fairly short period of time, four months or so, for at least a year thereafter in this exquisitely susceptible animal you would have no evidence whatsoever of the continued presence of that infection.

DR. SCHMIDT: This is quite right.

DR. MCDERMOTT: So that, in reference to the situation that Dr. Lincoln was considering, if the baby had been infected quite recently, a four-month period of therapy in a baby, assuming that the time sequences were the same, might well be all that would be necessary.

DR. SCHMIDT: I think so, if one can translate the observations from one exquisitely susceptible primate to another relatively susceptible primate.

DR. MCDERMOTT: How do you feel about this situation, Dr. Canetti?

DR. CANETTI: May I first ask a question of Dr. Schmidt? In this last experiment did you infect your monkeys with very small dosages?

DR. SCHMIDT: Yes, they were infected with between 500 and 700 viable units, Dr. Canetti.

DR. CANETTI: This is a dosage which is very small, but probably a little higher than the dosage that would be acquired in spontaneous infection by an exposed child.

I feel that the new results given by Dr. Schmidt are extremely important because they show that, after all, what must have happened in these monkeys, provided that sterilization has really occurred, is that, compared to the other situation which he had described two or three years ago, these bacilli just probably passed out spontaneously.

This is very important and this presents hope for real sterilization after short treatment of an infection which is acquired and which is treated immediately, provided isoniazid is given immediately.

DR. MCDERMOTT: In other words, this is the exact parallel of the laboratory accident.

DR. CANETTI: Yes.

DR. MCDERMOTT: This is the exact parallel of the laboratory accident in which the technician injects his or her finger with a needle heavily contaminated with tubercle bacilli and, if isoniazid is then started, it might make sense. In other words, it might make more sense to start isoniazid immediately in such a situation than it would to allow the person to go along and see if he had developed a tuberculous infection. You would agree to that?

DR. CANETTI: Yes.

DR. MCDERMOTT: Dr. Raffel, how do you feel about the idea that a four-month period of therapy in a four-month-old exposed child would be reasonable on the basis of these theoretics?

DR. RAFFEL: I don't think this is a subject that one should have feelings about. If there is evidence to suggest, as Dr. Schmidt just said and Dr. Lincoln indicated, that this can be effective in sterilizing the tissues, then I think obviously it is the thing that should be done. I must confess that these results of Dr. Schmidt's are somewhat opposed to earlier ones in monkeys in which infection is brought about by spontaneous means; that is, by simply subjecting monkeys to other monkeys that already had tuberculosis. But, as I say, I think this is a matter in which emotions play no part. If the evidence indicates this, then obviously it is the correct thing to do.

DR. MCDERMOTT: I think it is true, though, isn't it, that the situation that we were posing for Dr. Lincoln and the situation we were posing for Dr. Schmidt, or that Dr. Schmidt was posing, are somewhat different in that the four-month-old child could have had an infection one day old or four months old, whereas the monkeys could have had an infection only one day old. Indeed, when the monkeys had had infection for a longer period, it didn't work as well.

DR. SCHMIDT: No, I don't think we have information on that point and I don't think this should be the interpretation. When one has to wait only a week and a monkey is really infected, then one is not dealing with prophylaxis, it seems to me, but with therapy.

DR. MCDERMOTT: I am afraid I don't follow you.

DR. SCHMIDT: If I understood you correctly, what you are saying is that we began treatment on the day the animals were inoculated, which is quite correct. On the other hand, in Dr. Lincoln's situation, the infection may have been acquired a number of days, or even weeks before, but not for a sufficient period of time to allow tuberculin conversion.

DR. MCDERMOTT: Yes.

DR. SCHMIDT: There you are really talking about therapy, Dr. McDermott, I think, and we are talking about prophylaxis. We're getting into this exercise in semantics again, but I think you have to distinguish between them.

DR. MCDERMOTT: The simple way to get yourself out of the semantics question is to just indulge in more semantics, and so instead of saying primary prophylaxis is the prophylaxis of the as yet uninfected host, we will just change it to primary prophylaxis is the prophylaxis of the as yet *undemonstrably* infected host, because that is the situation we face.

In other words, it is akin to your first experiments, in which you put the monkeys together. You don't know whether they had had the disease for one year or one day.

DR. SCHMIDT: This is quite right, but I think I would like to make clear what the difference in the situation was in these two studies, Dr. McDermott. In the first study that we talked about and which has been bandied about, the animals were exposed to heavily infected individuals right to the day when isoniazid was withdrawn. There is no reason to expect that they got more or less infected material from the infected animals during their year's residence with them. They could have been infected easily one day or two days before they were withdrawn.

DR. MCDERMOTT: Or a longer period.

DR. SCHMIDT: Or a longer period, that is right. We might have been dealing with therapy there, and it is true that it does take a lot larger dose

of isoniazid to treat than it does to effect prophylaxis. Actually it is the order of about 50 to 75 times difference.

DR. MCDERMOTT: I gather that your point, Dr. Schmidt, is that, if you put tubercle bacilli into a monkey and then administer isoniazid on the same day, this is not treatment.

DR. SCHMIDT: This is my thesis.

DR. MCDERMOTT: This is not treatment, then?

Dr. Lincoln, how do you explain the cases published by Dr. Lelong in Paris? I refer to the cases in which the children had been exposed to tuberculous mothers and then were removed from them and put on isoniazid for periods as long as four months. Then after cessation of therapy the children became tuberculin positive.

DR. LINCOLN: I think that simply means that the children were in the incubation period of primary tuberculosis when the isoniazid was first administered, and, as Dr. Baldwin showed with streptomycin, the administration of a drug early in the incubation period prolongs the incubation period.

May I make one point about what I said originally? When I said I treat them for four months I meant that I would use isoniazid for four months *as primary prophylaxis*. In other words, I would try to cover the period in which they might be incubating a primary tuberculosis which they had already received and, if I were sure then that they had not already developed primary tuberculosis, I would stop the drug and go on with vaccination.

If I thought that the child had actually developed a positive tuberculin with or without an X-ray picture or primary tuberculosis, I would not stop at four months.

DR. MCDERMOTT: You would go ahead then.

Dr. Youmans, have we any information on the administration of BCG to an animal with a latent tuberculous infection, an infection in which tubercle bacilli could be present in the tissues in small numbers and in a latent stage and the animal not be demonstrably reactive to tuberculin? In short, what would happen if you gave BCG to Dr. Lincoln's child at the end of the four-month period of therapy in case the therapy had not eradicated all organisms?

DR. YOUMANS: I don't know of any specific work on this point. Perhaps somebody else does know of some specific experimental work, but, so far as I can see, in such animals or human beings, if they are not under cover of isoniazid therapy they should develop an immune response the same as others. Under cover of isoniazid there is, of course, conflicting evidence regarding whether that interferes with the immune response.

DR. MCDERMOTT: Suppose you administered isoniazid for a four-month period to a child who was tuberculin negative when you started—but in actuality happened to be infected with tubercle bacilli. You then stopped treatment and the child was still tuberculin negative and you wished to give him BCG. Can you have the same assurances that tuberculin negativity means tuberculin negativity in that situation as you can in the ordinary course of events.

DR. YOUMANS: If a person is tuberculin negative, he is tuberculin negative. I am not sure I am getting your point here. If BCG vaccination is given and he becomes tuberculin positive, you are assuming that is the result of the vaccination and not from some latent infection which has developed in the meantime. I can't see that it makes any difference, myself.

DR. MCDERMOTT: Let me put it this way then: If a person is infected with tubercle bacilli, is there risk in giving BCG in that situation?

DR. YOUMANS: Personally, I don't see why there should be; no.

DR. MCDERMOTT: I am interested to hear that, and I think we should discuss that point. It is generally stated that there might be, though.

DR. YOUMANS: Yes, vaccination in the face of a known infection, and so forth, is not usually considered good, but this situation is one in which (at least the situation that you propose) there might theoretically have been an infection, but there was no evidence of it. So I would say then let's accept the evidence which points to no infection and go ahead and vaccinate, and I don't see any reason why it should be deleterious at all. In fact, I don't see why one couldn't vaccinate at the same time one was giving isoniazid, as far as that is concerned, except for some of the evidence which tends to indicate that the vaccination procedure would be less effective under those conditions. I am not convinced myself that it would be, but there is evidence which would point to that.

DR. MCDERMOTT: So really your position is that, in the first place, BCG in the presence of tuberculin hypersensitivity may not necessarily be such an awful thing at all and the relatively few instances in which you have a few tubercle bacilli around the premises but not enough of an

active infection even to get a positive reaction shouldn't present any particular problem.

DR. YOUMANS: To me at least it would not.

DR. MCDERMOTT: Thus far we have been devoting our attention to the questions of primary prophylaxis and of what might be called some of the basic theoretic and practical implications of that. I would say that the situation is that certain members of the panel have expressed the belief that this is a sensible thing to do, with due realization of the disadvantages, and that from both Dr. Lincoln's feelings and Dr. Schmidt's interpretation of his experiments there is hope that possibly short periods of prophylaxis in an exposed person who is removed from exposure may be all that is necessary.

Then on top of that is Dr. Youmans' opinion just expressed that in that situation, if a few subjects had slipped by and still had a few tubercle bacilli in them, the administration of BCG per se would not seem to be a very serious problem.

Could we go on then to *secondary prophylaxis*, namely, the use of isoniazid or any other drug in the host who is already infected as evidenced by a positive tuberculin reaction.

Dr. Raffel, consider your three points against prophylaxis at the primary level, do you believe they have validity here in the secondary level?

DR. RAFFEL: No, I don't think so. I think at the secondary level we are dealing with a subject who has developed as much immunity as he is capable of. He has acquired everything he can acquire against the bacillus. Consequently, it seems to me there are no cons in this case except, of course, such cons as might arise from practical considerations, that is, can you catch hold of this individual and keep tabs on him and give him isoniazid for a long enough period to be effective.

I might say while I have an opportunity that I would like to line myself up, as I think I did in my original presentation, with those who think that in the primary situation the pros certainly outweigh the cons.

DR. MCDERMOTT: I thought I was recording you that way.

Dr. Holm, could I ask you to return to this question for a moment of the administration of BCG to an infant already treated with isoniazid who, nevertheless, might still have a few tubercle bacilli in him. Do you agree with Dr. Youmans that this is probably not much of a problem?

DR. HOLM: Yes, absolutely.

DR. MCDERMOTT: Good. May I say in passing to this secondary prophylaxis that I do not agree with much of what has been said in that I think that the evidence that Dr. Raffel already presented at the beginning is quite impressive, to the effect that it is possible to treat an infection too early. This is seldom possible in clinical practice because one has to have the infection in a recognizable form and that is not too early. But when one is administering drugs to babies exposed to tuberculous mothers, babies who have not as yet shown evidence of disease, one could conceivably be treating the infection too early. By too early, I mean a situation quite analogous to what happens in scrub typhus, to what happens in Q fever, to what happens probably in syphilis, and to what apparently happened to Dr. Lelong's babies in Paris; namely, you just freeze the situation, do not get rid of the tubercle bacilli. They stay there in some and in others they may get tired and go away, but over a period of many months they stay there, and when the drug is discontinued they can come back. This is a situation more analogous, I think, Dr. Schmidt, to your original monkeys, in which it did come back.

On secondary prophylaxis, then, your points, Dr. Raffel, are that acquisition is no problem there because they have already acquired it and the host reactions should have taken place. Could I make that question more precise? Do you believe that someone who has a positive tuberculin reaction has developed all of the acquired immunity that he is going to be able to acquire?

DR. RAFFEL: As you know, Dr. McDermott, that is not a fair question.

DR. MCDERMOTT: I said *believe*.

DR. RAFFEL: The general consensus nowadays, I think, is that the positive tuberculin reaction in itself is not the mechanism, that is, positive tuberculin reactivity is not the mechanism of acquired immunity to tuberculosis. On the other hand, it serves as an index of the fact that the subject has responded immunologically to the bacillus.

What the mechanism of immunity to tuberculosis may be is still a moot question. Perhaps some change takes place in the macrophages. Perhaps there are other ways in which this is brought about. It may be a combination of circumstances. But, on the basis of all that we know about host-parasite infections in general,

I think it is logical right now to assume that a person who has responded to the bacillus with the positive tuberculin reactivity has responded to his fullest extent in other respects also, and that he has all the acquired immunity that he is going to be able to acquire.

DR. MCDERMOTT: Just to get the record straight, let us assume, now, that the tuberculin reaction is a positive reaction; when we talk about a positive tuberculin we are talking about something that everybody understands.

Dr. Canetti, do you agree that, with respect to acquired immunity, the person with the positive tuberculin reaction represents one in whom everything that is going to happen has happened by that point, the same position expressed by Dr. Raffel?

DR. CANETTI: I am afraid I don't agree exactly. I think that there is some experimental evidence that usually tuberculin sensitivity appears earlier than acquired immunity, or, let us say, that tuberculin sensitivity reaches a peak earlier than acquired immunity.

I think from some old experimental evidence —work on guinea pigs—that treating an infection just at the moment conversion occurs would probably mean treating it at the moment when the maximum of acquired immunity is not yet present.

I wouldn't say that this is an absolute argument against treating at this moment, but we should realize that, if we treat at the very moment of conversion, at the early moment, the full immunity might not be present.

DR. MCDERMOTT: How do you feel about treatment in the situation discussed earlier with primary prophylaxis in that respect?

DR. CANETTI: It is a very difficult question. I think this is a problem of special situations. If we were sure that we could get rid of the bacilli by primary prophylaxis, it should be done in a situation in which exposure is not very heavy; and in other situations in which exposure is heavy, primary prophylaxis should, of course, be done, but only with the addition of vaccination. This is my opinion.

DR. MCDERMOTT: You feel, then, that a primary prophylaxis would obviously interfere with any acquisition of immunity because, if it worked, there wouldn't be a chance.

DR. CANETTI: Certainly.

DR. MCDERMOTT: This is also the crux of the situation in the secondary prophylaxis, isn't it, just that, namely, whether when you treat somebody with a positive tuberculin reaction you run a risk of seriously suppressing acquired resistance that he might acquire thereafter, or whether everything that is going to happen in terms of immunity has happened by then and you are safe and can go ahead with your therapy?

DR. CANETTI: If you treat early, at the moment of conversion, then the situation may hold; but if you treat a person later on who has converted three months previously, or something like that, the situation is already entirely different. Then I don't think that you seriously interfere with the acquired immunity; but then the problem is one of the possibility of eradicating these bacilli from the host at that stage.

DR. MCDERMOTT: In such a case, then, Dr. Canetti, somebody whom you treated three months after he had converted and you treated him for a year and then stopped, would he be in as good shape with respect to future exposures to tubercle bacilli as somebody who had healed his primary infection by natural means in the same period?

DR. CANETTI: I can't give you a definite answer on that because there is no positive evidence. In my opinion in all likelihood if somebody hasn't been treated too early—say, for instance, somebody has been treated three or four months after infection and he has even been treated for a long time—I don't think that his immunologic condition would be significantly different from that of somebody who has not been treated.

DR. MCDERMOTT: Dr. Youmans, how do you feel on these two points?

DR. YOUMANS: I think there is a basic point here on which the comments of the speakers have been made. It occurred to me that we are sort of talking around the circle a little bit here. In the first place, we talked about chemoprophylaxis, whether primary or secondary, and the purpose of that chemoprophylaxis is to inhibit the multiplication of tubercle bacilli in tissue or to kill them, or perhaps both. There is some evidence from what Dr. Schmidt has said, and I think there is some other evidence. Dr. Zorini reported that calves, for example, that were given isoniazid and exposed to infected cattle did not become tuberculin positive.

There is, then, some evidence to indicate that isoniazid, at least when acting prophylactically upon minimal infection, may completely eradicate tubercle bacilli, at least to the point where no

hypersensitivity develops. Therefore, if isoniazid is a drug which can do that, the problem of whether it is used in such a manner as to permit the development of immunity or not becomes no problem at all. It is rather pointless because, if we have a drug which will eradicate tubercle bacilli, then we don't have to worry about whether the person develops immunity or not.

We are only concerned with the problem of whether immunity develops or not if the drug is not adequate, if tubercle bacilli are not eradicated in certain situations, or if there are going to be subsequent situations in which that person may; be exposed to infection when he cannot get chemoprophylaxis.

If this is the case, if the latter situation is the one that really pertains, one should really give much more serious consideration then to vaccination, at least for primary prophylaxis, than to chemoprophylaxis; so if chemoprophylaxis is really effective, whether immunity develops or not is not important except under the special situations I have mentioned.

DR. MCDERMOTT: But do you seriously believe, Dr. Youmans, that isoniazid eradicates infection in somebody who has had a positive tuberculin reaction for three months?

DR. YOUMANS: No, I do not.

DR. MCDERMOTT: That is the situation we are talking about.

DR. YOUMANS: Insofar as primary prophylaxis is concerned, we have some evidence that it may; but even in the person who has a positive tuberculin reaction if the drug is, let us say, completely suppressive, then whether immunity develops or not may or may not be important. It becomes important only when one withdraws the drug, which implies that the drug cannot be given indefinitely. Then, of course, we must rely upon the acquisition of immunity.

DR. MCDERMOTT: If there were some immunity that were going to develop and we prevented it with the drug, and the person's tuberculin reaction did not convert, as will happen in a majority but not in all cases, you are left with somebody with a positive tuberculin reaction, a year's treatment of a primary infection, and you can't give BCG.

DR. YOUMANS: Yes, but if you can keep on giving the drug forever it may not matter whether the immunity develops or not. This is a purely academic point I am dwelling on, but I would like to straighten out our thinking, that is all. If you are going to withdraw the drug and rely upon the defenses of the host, then you can't interfere with immunity or you have to immunize in some other way.

DR. MCDERMOTT: Dr. Middlebrook, how do you feel about this point?

DR. MIDDLEBROOK: We have just completed a series of experiments on guinea pigs on isoniazid prophylaxis against air-borne infection with a variety of dosages of tubercle bacilli by the air-borne route from two or three or four for a guinea pig through twenty-two, an average of twenty-two up to fifty-eight tubercle bacilli per animal. We studied stock laboratory strains. We also studied five wild strains of tubercle bacilli and freshly isolated isoniazid-susceptible strains.

DR. MCDERMOTT: Do we have the range of the number of tubercle bacilli, a range from two or three tubercle bacilli?

DR. MIDDLEBROOK: As a matter of fact, in the experiment in which we controlled the strain of organism and the size of the infecting dose, we used between two, three, or four organisms up to fifty-eight organisms, and treated with isoniazid for ten days only beginning the day before the exposure. We achieved the following: With fifty-eight organisms per animal, eight of twelve completely escaped infection, that is, they were still tuberculin skin-test negative and had no evidence of any tuberculous infection when they were sacrificed at 206 days after infection.

Among the second group that was exposed to only twenty-two tubercle bacilli, a larger number —that is, ten out of twelve—were completely protected. Among that group, of which there were twelve, that were exposed to the order of two, three, or four organisms per animal, all twelve escaped infection.

Now, the most interesting aspect of our results, I think, is that for those animals that did not escape infection, the development of skin hypersensitivity and evidences of infection did not appear as rapidly after cessation of treatment as one would have anticipated if one bacterial cell or two bacterial cells had not yet been sterilized.

DR. MCDERMOTT: In other words, four of twelve on the fifty-eight-organism dose in which the tubercle bacilli persisted took a long time getting tuberculin positive after drug administration was stopped.

DR. MIDDLEBROOK: Yes, and I think that is quite relative to the discussion that Dr. You-

mans and you have been presenting, namely, that it might well be possible, after interrupting isoniazid treatment, to sort of get ahead of the game in a fashion which would not be possible except under these circumstances, by vaccinating with BCG, not necessarily with an isoniazid-resistant strain or species. This might well get you ahead of the game. There might still be relapse in the sense that you might not have killed all of the bacterial cells, every last one, but the BCG vaccine should give you more protection in spite of the fact that the animal already harbors living tubercle bacilli than it would under ordinary circumstances. I thought this might be of some interest.

DR. MCDERMOTT: In short, the animals have some bacilli in them, but they are obviously not many or not very serious at that moment, and BCG should be able to take care of that.

DR. MIDDLEBROOK: They are not drug resistant and they are not attenuated organisms genetically because, when they are isolated from the animals that ultimately do develop massive tuberculosis in all cases with a fully pathogenic infecting strain, they are still fully pathogenic.

DR. MCDERMOTT: The other side of this coin, though, is the gloomier side, and that is that the four animals did have tubercle bacilli in them and did not have positive tuberculin reactions and, as these bacilli are pathogenic potential, is it not possible (to return to Dr. Lincoln's babies) from your experiments to infer that, if you stop therapy at a four-month period in a number of children who had not been tuberculin positive when you started, some of those children will be harboring tubercle bacilli within them?

DR. MIDDLEBROOK: In terms of the numbers of tubercle bacilli to which children are exposed, as judged by the rate at which children develop tuberculin hypersensitivity, let us say, in a household in which there is a tuberculous patient excreting fully pathogenic tubercle bacilli, we might assume that a single unit, that is, one tubercle bacillus, is what usually initiates the infection. In these circumstances, it would seem to me that the clinical results should be something of the order of what we obtained when we exposed the animals to only two, three, or four organisms, that is, something closer to a hundred per cent; in other words, analogous to what Dr. Schmidt stated.

These animals had only ten days of treatment with the drug, and I think it is fair to anticipate that isoniazid prophylaxis against the infection, which is what you call *primary prophylaxis*, will be quite remarkably effective. The problems, however, of public health application of this, I think, are problems that Dr. Youmans indicated when he pointed out that there are practical aspects of the problem (anthropologic and psychologic) that go beyond the purely scientific aspects.

DR. MCDERMOTT: Isoniazid as a primary prophylaxis would be effective if you could give it on the same day as infection. Thus far all our laboratory evidence is to that point.

DR. MIDDLEBROOK: Incidentally, an error was made by a technician and isoniazid was administered in one single dose of 40 milligrams per kilogram on the third day to a group of guinea pigs. This resulted in cutting down the number of primary pulmonary tubercles fivefold, so that one single dose of isoniazid really has a rather striking sterilizing activity. One animal in this group, however, escaped infection, but the number of primary pulmonary tubercles was cut from an average of fifty-five to eleven.

DR. MCDERMOTT: Do you believe, Dr. Middlebrook, that, if your animals had been exposed for a longer period, the ten days of isoniazid therapy would have produced those results?

DR. MIDDLEBROOK: Exposed for a longer period?

DR. MCDERMOTT: Suppose they got fifty-eight tubercle bacilli one week and were put on isoniazid three weeks later, comparable to what might happen in the home.

DR. MIDDLEBROOK: In point of fact, if we initiated the isoniazid treatment ten days after the exposure, in no instance yet have we ever observed eradication of the infection. When we stopped the isoniazid treatment, the infection in the guinea pigs relapsed.

DR. CANETTI: I think this is probably what you have observed; but others have observed that, even if treatment is started three weeks after infection, some guinea pigs will reach absolute sterilization. This is a question of proportion.

DR. MIDDLEBROOK: And length of period of treatment?

DR. CANETTI: Yes, of course.

DR. MCDERMOTT: Could we leave the situation at the moment as follows, namely, that there is evidence that, if one gives isoniazid *at the same time as the infection* and the infecting dose is small,

appropriately small, in periods of follow-up of the order of 200 to 365 days off treatment everything looks well; that, if one infects the animals at some period *before* the isoniazid administration—say, ten days, two weeks, or two months—the evidence that one can eliminate the tubercle bacilli uniformly is no way nearly so good.

Dr. Canetti, could you give us a rough idea of how many tubercle bacilli go into the lung probably when somebody develops a primary infection?

Dr. Canetti: This has been a highly controversial point, but there are two main theories which are not very different for this situation. One is that of Bruno Langay and Chaussay, who maintained that only single units, of one, two, or three bacilli, can reach lung alveoli under normal conditions. This was opposed on some ground by Rich who maintained that the number might be higher, but even he didn't admit that these numbers might be higher than a hundred, two hundred, or something like that. It would never go into more than that. That is the number of bacilli which might reach the lung at one time.

Dr. McDermott: How many bacilli would you find in a completely circumscribed caseous lesion, one centimeter in diameter?

Dr. Canetti: In many cases you wouldn't find any; you would find perhaps ten, twenty, fifty on an average.

Dr. McDermott: How about a progressive lesion, the edge of a progressive lesion?

Dr. Canetti: If the lesion is softened and opened into a bronchus, this is entirely different; then the figures would reach hundreds of thousands or even more.

Dr. McDermott: Dr. Holm, what is your feeling on this point of the suppression of acquired immunity in the tuberculin-positive person? Do you think there is danger that we would be leaving these people in a worse state than if they had been allowed to heal their primary infection by natural means?

Dr. Holm: I don't think I can contribute to this point. I have no further evidence to quote.

Dr. McDermott: When do you think infection takes place in the home in the presence of a donor who is highly infected?

Dr. Holm: The interesting thing there is that many of the children can live in a household with infectious persons without being tuberculin positive, so that the chance is not too high. I think you have to recognize that tuberculosis is much less infectious than many other diseases. Even when a mother has an open case of tuberculosis there are cases in which the children can reach the age of two or three years and still be tuberculin negative.

Dr. McDermott: Dr. Robson, how do you feel about this point of suppression of acquired immunity after infection has taken place?

Dr. Robson: I don't want to encroach on the things I am going to say tomorrow, but I am perfectly convinced from my own work that, if you have established the infection in mice and produced immunity, then treatment with isoniazid would suppress the immunity.

Dr. McDermott: If you have established an infection in mice—

Dr. Robson: And you have tested and immunity is present—

Dr. McDermott: If you are certain immunity is present, and you then give isoniazid, you will affect that immunity?

Dr. Robson: Quite definitely, yes; in a period of five months the immunity will have almost completely disappeared.

Dr. McDermott: And the control mice, of course, do not have the ability to heal the infection?

Dr. Robson: No, and the immunity would be present for periods of well over a year. It may be a lot more, but that is the sum total of the period for which we have studied it. So there is no question in my mind that, under the specialized conditions under which we have worked, treatment with isoniazid does, in fact, decrease and lead to the disappearance of immunity.

Dr. McDermott: So we are then faced with the practical question: If this should happen in humans, is it a serious enough thing to keep us from going ahead with it, unless we supply the immunity artificially by BCG or some other form of vaccination?

Dr. Robson: Speaking again essentially as an experimentalist, my view is that it *is* a serious problem, this problem of the suppression of immunity. From my own experience, I certainly wouldn't be prepared to use isoniazid without at the same time looking for methods of artificially supplying immunity.

Dr. McDermott: That poses the question, and I think it is a good one to poll the members of the nuclear panel on this point—

Dr. Robson: May I just add one other point, because I think it is very relevant. It has been

suggested that you might supply immunity by treating the patient with an isoniazid-resistant BCG during the period of isoniazid administration. Again experimentally, you know very well that H37Ra does not multiply in the mouse, and H37Ra will in fact produce immunity in the mouse.

If you infect the mouse with H37Ra and treat it with isoniazid, then immunity will no longer be produced. I don't know quite why that should be the case. These are results we haven't published yet because we are so worried about it, in a way. We don't want to report it until we are completely satisfied. But, as far as our experiments have gone, the administration of isoniazid following an infection with H37Ra will suppress the immunogenic properties of that strain. Thus we must consider very seriously whether any strains of any bacillus given to the human being during the period of isoniazid treatment will in fact supply immunity there. Again, I would like to say that we should be extremely cautious in taking an allergic reaction as evidence of the degree of immunity present. That is another question.

DR. MCDERMOTT: We should be extremely cautious in what, Dr. Robson?

DR. ROBSON: In assessing to what extent an allergic reaction is an expression of immunity. Of course, I am sure you are aware of that.

DR. MCDERMOTT: Dr. Canetti was, so far as I recall, the first person who suggested the use of isoniazid-resistant BCG in this situation, and both in his laboratory and in Dr. Middlebrook's laboratory work has been done on this subject. I believe, Dr. Canetti, you found in experiments in guinea pigs that the guinea pigs immunized with the isoniazid-resistant BCG and then treated with isoniazid did as well as with the wild type of BCG, and that was the experience in Dr. Middlebrook's laboratory, too.

DR. MIDDLEBROOK: I would like to ask Dr. Robson a question. Did you equate the infectivity or pathogenicity of H37Ra with an isoniazid-resistant mutant strain of BCG, Dr. Robson?

DR. ROBSON: I am afraid I can't answer that question.

DR. MIDDLEBROOK: What dose of H37Ra did you use in your mice?

DR. ROBSON: Something of the order of 10,000 organisms.

DR. CANETTI: I think the whole problem whether isoniazid inhibits the development of immunity is a problem of the numbers of bacilli you inject. In experiments in which you inject high numbers of bacilli and you treat immediately with isoniazid, you get an immunity. This has been shown by different investigators. If you inject a high dosage of BCG, normal, not isoniazid-resistant BCG, and you treat immediately with isoniazid, you get quite a satisfactory immunity and there is no inhibitory action; but, if you inject with very low numbers of BCG, then, of course, the multiplication of these bacilli is stopped and there is no sufficient antigenic stimulus to build an immunity. So I think the whole problem is a problem of numbers.

DR. MCDERMOTT: If you are using large enough numbers, you are really giving a partially killed vaccine.

DR. CANETTI: Yes; there has to be a great number.

DR. MCDERMOTT: If you give an awful lot of bacilli, whether they are dead or alive, they will, nevertheless, immunize. We have heard, then, opinions to the effect that the administration of isoniazid after the acquisition of infection might affect immunity if it were done right away, at the moment of conversion, but probably does not affect immunity thereafter. An exception would be Dr. Robson's animal experiments, which would indicate the contrary.

May I poll the individual members of the nuclear panel, then, as to whether they are fearful of this point, sufficiently fearful, so that they do not favor the administration of isoniazid to persons with positive tuberculin reactions? Could I start with you, Dr. Lincoln?

DR. LINCOLN: I think practically that would hardly ever occur in children because by the time you get a positive tuberculin test you usually have well-established disease. It might occur in the very occasional case such as Dr. Robson described, in which while selecting children for BCG vaccination the conversion was observed within a period of a few weeks and treatment would be started immediately. But I think it would occur only very rarely in practical cases.

DR. MCDERMOTT: Then would you favor giving isoniazid to children who are found to be tuberculin reactors, even though you don't know how long they have been positive?

DR. LINCOLN: With no evidence of tuberculosis otherwise? I would think that any child who has a known conversion, say, within six months should be treated. In practical terms, that would

mean that you would treat all young infants. And I would add that I would treat adolescent girls because of the fact that, even without any other evidence of tuberculosis, you may find evidence of pulmonary spread.

DR. MCDERMOTT: How about nine-year-old boys?

DR. LINCOLN: In the in-between age I would not treat every child.

DR. MCDERMOTT: And the reason you would not?

DR. LINCOLN: I think it would be practically impossible to treat every child even in this country when you found a positive tuberculin reaction and you didn't have any idea how long he had had it. In countries where there is much more tuberculosis, it would be absolutely impossible. I think every case should be considered individually in the actual practice of medicine. I think there are some patients whom you might want to treat for various reasons, but I would not treat every child.

DR. MCDERMOTT: Would the size of the tuberculin reaction—if the area of induration is greater than 10 millimeters—would that influence you in a nine-year-old boy?

DR. LINCOLN: It wouldn't so far.

DR. MCDERMOTT: Dr. Raffel, what is your position on this matter? We realize that we are talking on the basis of theoretic considerations.

DR. RAFFEL: Certainly so far as the practical aspects are concerned, I don't think we can get a better opinion than Dr. Lincoln can give us as to which age groups should be given the benefits, if any, of isoniazid after tuberculin positivity has been established. If immunity is lost as a result of this practice, the only basis I can possibly conceive of would be that the infection has been completely wiped out. If the infection is completely wiped out and the immunity is concomitantly lost, that is not an undesirable result. Of course, you then have to face the problem that the individual might become reinfected. On the other hand, we then go into a much different age group in which the question of reinfection is not such an important matter.

I would cast my ballot with qualifications of age, and so on, that Dr. Lincoln has mentioned for treatment of such persons, for treatment of the tuberculin-positive persons without special fear that they will lose their immunity, assuming that their loss of immunity means loss of bacteria which are able to stimulate immunity.

DR. MCDERMOTT: So that your position would be that you might not treat a nine-year-old boy, or you might; but in making that decision you wouldn't worry about doing him harm.

DR. RAFFEL: That is right.

DR. MCDERMOTT: Dr. Holm?

DR. HOLM: I would be prepared to treat prophylactically with isoniazid children who show positive tuberculin reactions if they were less than two or three years. For persons over that age I would reserve my judgment because there has been a big-scale experiment in which there are large groups of reactors of all ages under prophylactic treatment, half of whom get treatment and half get placebo. Until we have the results of this, I don't think I would be prepared to give any advice on what should be done. When these results are in, I think we will be in a much better position to say what should be recommended.

DR. MCDERMOTT: Could you answer this, though, Dr. Holm: What are the chances of developing serious tuberculosis by a nine-year-old boy who has had a positive tuberculin reaction for a two-year period?

DR. HOLM: In my best judgment the chances are very small, so small that at present, if I was forced to give an opinion, I would say I wouldn't treat.

DR. MCDERMOTT: Would you say that the chances would be less than 3 per cent?

DR. HOLM: I would consider it much less than 3 per cent.

DR. MCDERMOTT: So that, if we are to use isoniazid in tuberculin reactors of all ages up through adolescence, we would be treating in some age groups 97 or 98 people who required no treatment for every 100 treated; is that correct?

DR. HOLM: Yes, and I would certainly like to treat them only at the young adult age, not to treat them at the age of nine; to treat them when the chance might be much greater of the development of clinical tuberculosis.

DR. MCDERMOTT: Then you and Dr. Lincoln both are suggesting treatment of the very young, during the first two or three years of life, and treatment during adolescence particularly in young girls; but between, say, the age of three and the onset of puberty, you advise treating on an individual basis; and your reaction in the last-named circumstances is seldom to treat, as is Dr. Lincoln's.

Dr. Canetti?

DR. CANETTI: My position is not very different. I would probably treat very recent converters and treat them for a short time.

DR. MCDERMOTT: How long?

DR. CANETTI: I can't say. If there is no clinical evidence, there is no point in treating somebody for a very long time for something which, if it leads to disease, would take no more time than for treating the disease. I would try to give him a sort of treatment just to protect, but this is only for —

DR. MCDERMOTT: You mean two or three months?

DR. CANETTI: Yes, something like that. A boy who has been a "converter" for a long time I would not treat except in families with many cases of tuberculosis or perhaps in cases of very strong cutaneous reactions to the tuberculin. I think there is a reason for treating those with strong reactions.

DR. MCDERMOTT: In other words, somebody with an induration of 10 millimeters in diameter or more you would be more apt to treat at any age?

DR. CANETTI: Yes; with a very strong reaction. I can't give exact figures, but it would have to be a very strong reaction which probably I would treat for a short time.

DR. MCDERMOTT: Do you think that antimicrobial drugs are active in the case of a tuberculous infection of two years' duration manifested only by a positive tuberculin reaction in a nine-year-old boy?

DR. CANETTI: I think we have no definite evidence on that, but I *believe* not.

DR. MCDERMOTT: You agree with Dr. Holm as to the relatively small danger from the natural infection in a nine-year-old boy in those same circumstances. Dr. Holm said that it was very low, less than 3 per cent, much less than 3 per cent.

DR. CANETTI: I absolutely agree with him.

DR. MCDERMOTT: So that we have a situation in this nine-year-old boy in which his chances of developing disease untreated are very small.

DR. CANETTI: Yes.

DR. MCDERMOTT: And you believe, but say there is no proof, that antimicrobial drugs probably are not active against tubercle bacilli anyway in such cases.

DR. CANETTI: Yes. I would say that a child of nine years of age whose tuberculin reaction was not particularly intense and had been present for two or three years has no more living bacilli in him. That is a belief.

DR. MCDERMOTT: Dr. Youmans, how do you feel on this point?

DR. YOUMANS: What Dr. Lincoln and Dr. Holm and Dr. Canetti have said I would in the main agree to. It seems to me we have a bit of a paradoxical situation here in which human beings become infected. We wish to control the infection with a drug, but at the same time we are scared to control it too much because they won't develop resistance which might in itself control the infection. Therefore, it is necessary in any situation to balance the risk of the development of active disease against the protection afforded by the resistance that they will have developed by the time they become tuberculin positive. If the risk of developing active disease is as low as Dr. Holm says —

DR. MCDERMOTT: At that age group.

DR. YOUMANS: I am limiting myself now to the age groups mentioned. I would see little reason for giving mass prophylaxis under these conditions.

DR. MCDERMOTT: Dr. Holm, what do you think the risk would be of tuberculosis developing in a nine-year-old boy who has become a tuberculin reactor within the past two or three months?

DR. HOLM: It is difficult, of course, to give exact figures, but it might come closer to your judgment of the 3 per cent or it might even be higher. It would depend a little on what you would call a case of tuberculosis.

DR. MCDERMOTT: It is a little bit like betting on two-year-olds at the racetrack. A three-year-old or a four-year-old horse has gone to the post a number of times and we know that, if over a two-year period he has been a winner, he is apt to be a winner.

Here, in the form of a recent converter, we have the equivalent of a two-year-old colt that may be a winner or may not be. Even here, however, the risk is not enormously great.

Dr. Schmidt, on the basis of theoretic information, how do you feel about this question of the treatment of human beings with positive tuberculin reactions and no other evidence of tuberculous disease?

DR. SCHMIDT: I think in this particular horse race I am going to be on the outside of the track, Dr. McDermott. The way I look at it is that immunity doesn't have anything nearly as good to offer compared with isoniazid treatment, and

I would be in favor of giving or administering isoniazid to very recent converters on the ground that the immunity that is purchased is not sufficiently solid to guarantee protection to a great number of these persons. I may have to modify that considerably by saying that immunity is not sufficient to protect a significant number of persons. I think this is a much better way of putting it. On the other hand, I think one can get this protection with isoniazid. I would rather take the chance on gaining my immunity at a later date and avoiding tuberculosis at this particular date, and so I would advocate the treatment of all recent converters.

DR. MCDERMOTT: How do you feel about the treatment of a tuberculin reactor under the age of twenty about whom you know nothing as to the date of infection?

DR. SCHMIDT: Here I think you can't say that you don't know anything about the date of infection because the epidemiology within the family group may be such that you may be able to predict how long this person has been exposed and how long he has not been exposed, and I think this would affect the decision as to whether you went ahead with prophylaxis or chemoprophylaxis or chemotherapy, or whether you did not.

DR. MCDERMOTT: Suppose, though, that this were an isolated finding, as it all too often is; that is, you find one child positive and you don't know the source.

DR. SCHMIDT: It costs little to give isoniazid. The drug is well tolerated. The evidence that you can develop drug resistance and inapparent infection is not at hand. I would be in favor of giving the drug.

DR. MCDERMOTT: Thus far, the nuclear panel has considered the possible dangers of the suppression of immunity here, but has stated that, despite various conceivable theoretic considerations, *on the whole*, they would favor going ahead with secondary chemoprophylaxis in certain situations. One situation on which there is agreement is the advisability of giving the drug to three-year-olds and younger infants; another agreement seems to be that it is advisable to use secondary prophylaxis in adolescence, particularly in girls. Between the three-year-old child and the adolescent, *individualization* seems to be the watchword, except in the case of known recent converters, who everyone agrees should be treated.

Dr. D'Arcy Hart, would you like to comment on this?

DR. D'ARCY HART: I would like to follow on from what Dr. Schmidt said and that is the practical situation, if you find children (and I would like to limit it to adolescents) who have tuberculin reactions, what are you going to do? I would say that we do have some good evidence from children (and in this the British Medical Research Council and the U. S. Public Health Service fortunately agree) that, on our part, fourteen-year-old children and, on their part, Navy recruits (a bit older, sixteen to eighteen) do show an incidence of tuberculosis markedly different according to the degree of sensitivity.

DR. MCDERMOTT: The size of the tuberculin reaction?

DR. D'ARCY HART: The size of the tuberculin reaction or the dose to which it responds. The difference is quite marked. The incidence of tuberculosis in these strongly tuberculin-positive children is so high that I feel that one is surely justified in giving isoniazid for several years to children of fourteen (I just take this age because we have the data) who are strongly tuberculin positive.

But then, contrariwise, you have those who are weakly tuberculin positive, whether that is due to nonspecificity or (as we believe in England at least) due to a low grade of tuberculous infection; it seems very unwise to use isoniazid as secondary prophylaxis in such cases. In other words, the low-level reactors and the intense reactors should not be bundled all together because, from our figures (and I think those also of Dr. Palmer), the less intense reactors have a comparatively low incidence of tuberculosis, not as low as if they had BCG, but pretty low. This suggests that they have some degree of immunity; and it seems that it would be a great mistake to give a drug which might interfere with that degree of immunity even though you might get a greater degree of suppression of the infection.

DR. MCDERMOTT: Would you repeat the age group?

DR. D'ARCY HART: Our age group is fourteen.

DR. MCDERMOTT: Nine to fourteen?

DR. D'ARCY HART: No, those at fourteen, who, in our country at any rate, are facing a period when the tuberculous attack rate and the morbidity are going to go up. In this particular situation, I think we have enough reason to take

the position that here and now you should divide them according to their degree of sensitivity, not lump them all together, and give isoniazid to one lot and not to the other.

DR. MCDERMOTT: Give it to the lot with the greater tuberculin reaction.?

DR. D'ARCY HART: Yes. May I have this chance now to ask one point, very short, on what has been said? It has been assumed from animal experiments that there is no danger of drug resistance developing, and I believe Dr. Canetti has figures for man too. What I want to know is can the nuclear panel reassure one that, if there are children such as I have just described, and you start a course of isoniazid treatment and they are highly tuberculin positive, possibly harboring a latent developing lesion which you can't detect from the X-ray, can you be sure that, if they don't take the treatment properly and only take it intermittently, there is no danger of resistant organisms developing should the treatment fail?

DR. MCDERMOTT: Would you be willing to qualify the question and not even bring in the point about intermittent therapy?

DR. D'ARCY HART: It is the intermittent therapy that I want to bring in because the animals don't have intermittent therapy. They haven't the opportunity.

DR. MCDERMOTT: This is a question which we certainly wish to have answered by the nuclear panel. I think I will express my own opinion first.

I think there can be no question about the fact that, if one treats enough children with positive tuberculin reactions with isoniazid—if one treats enough, somewhere, someplace—isoniazid-resistant tubercle bacilli will develop even though the treatment be quite regular; and the reason for that is this. In a certain number of cases there will be caseous tuberculous lymph nodes in the mediastinum which are not perceptible on the chest film. It might be by the reading of an expert like Dr. Lincoln, but to the average person familiar with reading chest films but not too familiar with reading children's chest films, a lymph node could exist that could perforate into a bronchus and then create, to all intents and purposes, a lymph-node cavity. You would then have a tuberculous cavity which you were treating regularly with isoniazid alone.

On that basis alone, Dr. Hart, I think we have simply got to assume that, if we treat enough persons, somewhere, someplace, there will be some drug-resistant strains. This merits consideration even when one is talking about secondary prophylaxis rather than the treatment of people with open cavities.

For the rest, in whom this particular pathologic situation does not occur, whether intermittent therapy would favor drug resistance cannot be so definitely decided. My own feeling would be that some degree of resistance would occur, but it would occur within the setting of a healing lesion and would not give rise to the discharge of drug-resistant bacilli.

I would like to hear from the members of the nuclear panel on this point because we have pretty well established how they feel on the subject of the case for the administration of primary and secondary prophylaxis. Now we must hear about the possible dangers of these procedures.

Dr. Canetti, do you wish to speak to that point first?

DR. CANETTI: In my opinion, there is very little probability of resistance developing in such a situation. The whole problem of resistance is related to the number of bacilli existing in the foci. In a true latent infection the number of bacilli existing in the foci is always extremely low and one doesn't see how this thing could change unless, of course, the infection became a true tuberculous disease with obvious manifestations. This is something different. We are speaking about treating latent infection.

I can't possibly imagine a case with sufficient numbers of bacilli in the foci of a latent infection which could lead to development of resistance. I have never seen one and I have had several resection specimens of cases which were more than latent infections, but with lesions close to them, only nodules but scattered ones—which is already distinct from the primary focus, and so on. And I never got a resistant strain out of this kind of lesion.

DR. MCDERMOTT: Dr. Youmans?

DR. YOUMANS: This point interests me because, while I agree with you that there probably would be some instances in which resistance would occur, I think they might be few. That is so not only for the reasons Dr. Canetti mentioned, but, if we look at the genetic mechanism of how these mutations occur, we have two entirely different situations in the active case with the open cavity. Not only do we have large numbers of tubercle bacilli there, but we have rapidly multiplying

tubercle bacilli which are subjected to the action of the drug. Here, there is more chance for the development of spontaneous mutants which are resistant to isoniazid and it is possible then for these to be selected.

However, in all of the children who are positive reactors and have no active disease, as Dr. Canetti says, there are not only very few tubercle bacilli, but the vast majority of those are nonmultiplying. I think one of the characteristic mechanisms of acquired host resistance is the inhibition of bacillary multiplication. These children also have some acquired resistance and, therefore, mutation is apt to occur less frequently, and isoniazid resistance, therefore, will not develop.

I might say that follows also from the experimental work that has been done along this line. Your own mice, Dr. McDermott, in which you get the persisters which are still isoniazid susceptible, you have been treating under conditions in which acquired resistance exists in the animal, and a lot of the inhibition to multiplication may be due to the acquired resistance as well as to the isoniazid.

DR. MCDERMOTT: Yes, I think without question that is the case. Is what you are saying, Dr. Youmans, that, in reasoning from animals to man on this situation, the nature of the lesion is all-important, and that in many of the laboratory animal experiments, except for those of Dr. Steenken (I want to call on him in a moment), the reason we do not see drug resistance in laboratory animals anywhere nearly so often as we see it in human beings is that we do not treat laboratory animals with established cavernous disease. Is that a correct statement?

DR. YOUMANS: Yes, that is exactly correct. In cavernous disease we have a situation in which tubercle bacilli can multiply which then favors mutation which favors selection.

DR. MCDERMOTT: And in the primary infection in the child who has not developed an obvious primary complex, the chances of cavernous disease are minimal except for the lymph-node cavity situation about which I spoke.

Dr. Steenken has been treating laboratory animals with established cavernous disease, and we should ask him about this.

DR. STEENKEN: You just stole a little bit of my thunder when you discussed the character of the disease, and that is what I was going to bring out: that in a lot of my experience the only animal in which I have ever been able to develop streptomycin resistance or isoniazid resistance, or resistance to any of the drugs, has been the rabbit. In the guinea pig or in the mouse we have not been able to.

DR. MCDERMOTT: Not even isoniazid resistance in the mouse?

DR. STEENKEN: No.

DR. MCDERMOTT: We can do that.

DR. STEENKEN: We haven't. I want to come down to the character of the disease. When we have produced miliary tuberculosis in rabbits, when they have acute disease, we have never been able to develop resistance even though we gave them massive intravenous infection.

DR. MCDERMOTT: Noncavitary disease, disseminated disease?

DR. STEENKEN: We never find resistance. If you produce cavitary disease, in those animals in which the cavities do not close you get resistance; but you can't predict it because you don't know which cavities are going to close. And you never can tell how resistant the strains are going to be in those animals. You can have highly isoniazid-resistant organisms that are catalase positive and you can have them catalase negative. So I really believe that the character of the disease is all-important.

Now that I have the microphone, I would also like to state that in some experiments that we have done we have used the hemagglutination test, not a tuberculin test in rabbits and guinea pigs to follow what is happening during the course of chemotherapy with respect to depressing the immunity. We have found that the hemagglutination ability goes down as the tuberculin sensitivity goes down.

In the back of my mind I had the thought that maybe we should put some more antigens back in the system to stimulate antibodies, so we used BCG. Here I can say that with massive doses of BCG the animals don't die, and an allergic reaction is not produced by it. We have not been able to increase their immunity by putting back either H37Ra or BCG.

DR. MCDERMOTT: And no treatment from that point on?

DR. STEENKEN: That's it. Just to see whether after you take them off the drug you can hold the disease in that stage. We are still working on it and, fortunately, I have Dr. Thurston, who is an immunologist, with me, and we are plugging pretty hard on this problem because I don't

think chemotherapy is the answer per se. You have to have something else to bring the host back into a normal immunity.

DR. MCDERMOTT: Do other members of the nuclear panel wish to add to these answers to Dr. Hart's question?

In effect, Dr. Hart, I gather that the feeling is that, reasoning from laboratory experiments and (in Dr. Canetti's case) from observations in human tissues, the chance of isoniazid resistance becoming a serious problem in the treatment of the child who is a tuberculin reactor but has no other evidence of disease is very slim. Indeed, the chief possibility is related to the possibilities of unrecognized cavernous tuberculous disease being present, which are very, very slim indeed.

Now we perhaps better change the question a little bit and say: What are the chances for the child who has an obvious primary complex? Dr. Canetti, how would you feel about that?

DR. CANETTI: About the resistance developing?

DR. MCDERMOTT: Yes.

DR. CANETTI: Very small.

DR. MCDERMOTT: Because the primary complex itself is not very apt to represent cavitary disease.

DR. CANETTI: The latent primary complex never shows cavitation and the number of bacilli is so small that resistance can't develop. The numerical factor isn't there.

DR. MCDERMOTT: And a nonlatent primary complex should be brought under treatment rapidly?

DR. CANETTI: Certainly.

DR. MCDERMOTT: So I gather, Dr. Hart, that the feeling is that, in general, the chance of drug-resistant bacilli emerging depends on the chances of having a big caseous lesion in communication with the outside, and, in the situation which we have been discussing, the likelihood of this is very small.

We should continue, then, on this point of possible dangers of chemoprophylaxis. We have considered two possible disadvantages: (*1*) that there may be a suppression of immunity; (*2*) that there may be drug resistance.

There seem to me to be only two more: (*1*) that we might be creating a whole mass of people who have not obtained the immunity that they might have obtained had their primary complexes not been meddled with; and the feeling seems here to be that that is not very serious as a danger.

(*2*) Then the other danger is the question of drug toxicity. Dr. Schmidt, how do you feel about the question of drug toxicity with reference to, say, a year's isoniazid administration in the various types of situations we have considered this morning, namely, tuberculin reactors?

DR. SCHMIDT: I think that the problem of toxicity of isoniazid is comparatively a small one. As with all drugs, you apparently get some allergic manifestations. I can conceive of situations in which the intake of things like B_6 is so low that the peripheral nerves might be damaged, but on the whole I think that the question of the toxicity of isoniazid in the doses that people are conventionally using is an unimportant one.

DR MCDERMOTT: As drugs go, it is remarkably nontoxic.

DR. LINCOLN: Clinically we see practically no drug toxicity to isoniazid even with dosages as high as 20 to 30 milligrams per kilogram. It has also been shown that there is no demonstrable pyridoxine deficiency in small children who are receiving adequate doses of isoniazid. I would not be afraid of toxicity, although I think that in the borderline group in adolescence we have to bear in mind the possibility of pyridoxine deficiency.

DR. MCDERMOTT: Dr. Lincoln, how many children received or were instructed to take isoniazid in the secondary prophylaxis studies with which you are associated? What is the rough order?

DR. LINCOLN: You mean the Public Health Service study?

DR. MCDERMOTT: Yes.

DR. LINCOLN: There were 2,750 children in the study and the number receiving isoniazid was, roughly, half. There were only a few cases in which isoniazid had to be discontinued and those were problems of vomiting, which might or might not have been due to the isoniazid.

DR. MCDERMOTT: Did any children have fits?

DR. LINCOLN: No.

DR. MCDERMOTT: Not a single instance of fits, as far as you know?

DR. LINCOLN: Nothing that they felt could be related; and in our studies at Bellevue, which now involve about 700 or 800 children, we have never seen an epileptiform convulsion that we thought was related to isoniazid.

DR. MCDERMOTT: Dr. Chaves, have you heard of convulsive seizures in children on isoniazid in your experience in the city of New York?

DR. CHAVES: No, I haven't, Dr. McDermott.

DR. MCDERMOTT: Dr. Holm, have you heard of convulsive seizures in any child in any large-scale program?

DR. HOLM: No, sir.

DR. CANETTI: I wish to add a word on something different, which is minor toxicity which may exist due to isoniazid even at low doses, for instance 300 milligrams a day; and that is a sort of mental intolerance—not exactly intolerance, but, for instance, students taking the drug and being unable to do real intellectual work. This is, of course, not a real toxicity. It is a sort of intolerance which has no importance if the problem is to treat patients, but it is a problem which might exist when it comes to the prophylactic use of isoniazid.

This is in our opinion one argument why isoniazid shouldn't be used widespread without due consideration for the type of prophylaxis which is needed.

DR. MCDERMOTT: Are there any other comments from the panel on this point?

DR. HOLM: I should like to confirm what Dr. Canetti has just said. In Denmark there are reports of exactly this type of toxicity. Doctors and lawyers and others of the intelligentsia who were under treatment complained that their memories were not as good as they had been. They had to make notes on everything instead of trying to trust their memories as they had been used to do. These symptoms disappeared as soon as the isoniazid was given up.

DR. MCDERMOTT: Is there a seasonal incidence? Is it worse in the springtime, Dr. Holm?

DR. RAFFEL: I would like to suggest that isoniazid be given to the entire legal profession!

DR. MCDERMOTT: The time has come to sum up. We have considered questions of primary prophylaxis and questions of secondary prophylaxis. With respect to primary prophylaxis, the consensus appears to be that there is a place for this procedure. This place apparently is in especially exposed people, particularly very youthful and especially exposed people.

There seemed to be a consensus, from which I dissented, that there was hope that in this situation one might have a high chance of uniformly eradicating tubercle bacilli with relatively short-term periods of isoniazid therapy in primary prophylaxis. This is something that obviously time will give us the answer to. Further comment on it, therefore, seems unnecessary other than to say that, when there is doubt, it is perhaps better to treat for longer than shorter periods.

Most of the discussion was on secondary prophylaxis which is, of course, a subject of much greater importance to us and of much more immediate practical importance. The feeling there, shared by all members of the nuclear panel, and with no dissent from the extended panel except for Dr. Robson, is that once infection has evolved to the point of recognition by, say, the tuberculin reaction, the chances are that everything that is going to happen in the terms of increments of host resistance has happened, and that the use of therapy at that point can probably be undertaken without too much fear that one is suppressing important increments of host resistance.

Both at the levels of primary prophylaxis and of secondary prophylaxis, there was considerable discussion on adding artificial immunization procedures at the time of, before, during, or after the chemical prophylaxis. I think I am correct in stating that all of the members of the panel who were in favor of primary prophylaxis in special situations and who are in favor of relatively short periods of such prophylaxis (four months or so) made the point that this should be accompanied by an immunization procedure and, to all intents and purposes at the moment, that immunization procedure would be the wild type, that is, the usual kind of BCG.

A most important opinion was presented on this point by several members of the panel, who are in a real position to know or to have a really informed opinion, to the effect that one need not worry too much about a Koch phenomenon to BCG in a situation in which there was no positive evidence of tuberculous infection and in which any tuberculous infection that might be present would be one in quite a latent state as a result of therapy.

It is perhaps too bad that we did not go into the question (as much as we might have) of what are these special situations for primary prophylaxis, but I gather that we were talking about infants and young children and perhaps adolescents undergoing heavy exposures, a greater exposure than, say, that occasioned by being a student nurse or a medical student.

With respect to secondary prophylaxis, namely, the treatment of the tuberculin reactor, all of the panel seemed to be of the opinion that this should be done in infants and in those below the age of three, even when one does not know the date of infection; and that isoniazid should be used in such situations during the first three years of life and during adolescence.

Between those periods of the first three years of life and adolescence, secondary chemoprophylaxis should be used on an individual basis. It was brought out that: (*1*) Many of these children are really not up against much of a threat in the first place; and (*2*) if their infection really is latent, isoniazid won't have much effect on it anyway. Dr. Hart made the further point that it perhaps might be wise to pay attention to the degree of tuberculin hypersensitivity, either the size of the reaction to a particular dose or the fact that any reaction occurred at all to a smaller dose. Thus, one might in one's individualization also choose to treat children who were neither infants nor adolescents, but were in the in-between age groups.

The final point made was that isoniazid is a remarkably nontoxic drug; that in adults it does perhaps have subtle effects which we have not yet fully perceived; but that, in terms of gross effects in children, the toxicity of the drug would not seem to be such as to militate against its widespread use. And Dr. Raffel in his introduction made the further important point that isoniazid does not interfere with the ecology, so to speak, of the situation; that it does not interfere with the other microbes in the flora so far as is known.

The panel seemed to be uniformly agreed that in the case of a recent tuberculin converter at just about any age mentioned (and we mentioned ages as high as twenty) they would favor the use of isoniazid immediately. Dr. Canetti suggested that maybe one would take the edge off the immunity; but he would, nevertheless, go ahead; the others believed they would go ahead anyway.

I think, then, I can sum up finally by saying that the theoretic considerations about primary prophylaxis do not bother the nuclear panel so much as they bother its chairman. But I, too, would agree that in some very special situations primary chemoprophylaxis might make sense, and we are all pretty much in agreement on what might be accomplished by the use of secondary prophylaxis.

May I thank the members of the nuclear and extended panels, and the audience.

PANEL TWO

ROBERTS DAVIES

HUGH E. BURKE

CARL MUSCHENHEIM

THEODORE L. BADGER

AARON D. CHAVES

J. R. BIGNALL

WILLIAM B. TUCKER

EDWARD H. ROBITZEK

PANEL TWO

THE HOSPITAL AND HOME: RESPECTIVE ROLES IN TUBERCULOSIS MANAGEMENT, INCLUDING THE CHEMOTHERAPY OF TUBERCULOSIS

Chairman: WILLIAM B. TUCKER
Introducer: AARON D. CHAVES
Panelists: THEODORE L. BADGER
J. R. BIGNALL
HUGH E. BURKE
ROBERTS DAVIES
CARL MUSCHENHEIM
EDWARD H. ROBITZEK

Dr. Tucker introduced the members of the panel:

Dr. Carl Muschenheim, Associate Professor of Clinical Medicine at Cornell Medical Center, and Attending Physician at New York Hospital.

Dr. Edward Robitzek, Director of Medicine at Sea View Hospital, and Attending Physician at Staten Island and Sea View hospitals.

Dr. Theodore Badger, Assistant Clinical Professor of Medicine at Harvard Medical School, and Visiting Physician at Boston City Hospital; and immediate past President of the American Trudeau Society.

Dr. Aaron Chaves, Assistant Professor of Clinical Public Health and Preventive Medicine at Cornell Medical Center; Supervisor of Clinics for the Bureau of Tuberculosis in New York City; and Assisting Attending Physician at New York Hospital.

Dr. J. R. Bignall, Senior Lecturer at the Institute of Diseases of the Chest, University of London, and Physician at the Brompton Hospital in London.

Dr. Hugh Burke, Assistant Professor of Medicine at McGill University; and Medical Director of the Royal Edward Laurentian Hospital, Montreal Division.

Dr. Roberts Davies, Director of the Florida State Tuberculosis Board, with headquarters in Tallahassee, for the four tuberculosis hospitals of the State of Florida.

The Chairman, Dr. William B. Tucker, is Director of the Tuberculosis Service of the Veterans Administration.

DR. TUCKER: The subject is known to you, as listed in the program, "The Hospital and Home, and Their Respective Roles in Tuberculosis Management, including the Chemotherapy of Tuberculosis." To point out some of the known areas of agreement and of disagreement, the panel discussion will be introduced by Dr. Aaron Chaves.

DR. CHAVES: Thank you, Dr. Tucker. In recent months a number of excellent articles have appeared which present a cross-section of current thought on the topic of this afternoon's panel. From these reports it is apparent that most authorities agree on the following points:

(*1*) Chemotherapy is the most important therapeutic tool in the management of tuberculous patients.

(*2*) It is desirable in most instances to start antituberculous treatment in a hospital.

(*3*) Isoniazid is the most effective of the antituberculous drugs and is used preferably in combination with other drugs.

(*4*) Chemotherapy should be continuously maintained for at least one year and, in most instances, for much longer.

(*5*) Indicated surgical intervention is best performed relatively early in the course of chemotherapy, certainly within the first twelve months.

(*6*) There is little place for pneumotherapy, that is, artificial pneumothorax or pneumoperitoneum, in the present-day management of tuberculous patients.

(*7*) Chemotherapy has radically altered previously held standards for the use of bed rest, occupational therapy, and rehabilitation.

(*8*) Effective chemotherapy permits earlier hospital discharge and return to work.

(*9*) Chemotherapy may be satisfactorily administered to selected groups of non-hospitalized patients.

There remains, however, a large area of disagreement, and it is the purpose of this afternoon's panel to try to narrow this down. As I understand the role of the introducer, it is for him to bring into focus for consideration by the panel the most important of the unsettled problems related to the assigned topic.

For the sake of completeness I have made no attempt to sharpen the subjects to be considered in the following discussion. There will of necessity be overlapping with some of the sub-topics taken

up by the panels to come on the following days. On the other hand, it may be of some help to know that the confusion into which I will throw this audience will be unraveled not only by the help of the present panel, but by the panelists to follow.

Among the controversial aspects of antituberculous chemotherapy, special attention is called to the following items:

1. The preferred combinations and dosages of drugs to initiate treatment, both for original treatment and re-treatment cases. Definitions of the terms "original treatment" and "re-treatment" I will leave for the panel to take up.
2. The indications for using isoniazid alone.
3. The duration of chemotherapy and indicated drug changes to be made during treatment; I think this should be taken up both for patients whose sputum rapidly becomes noninfectious as well as for patients whose sputum consistently remains infectious.
4. The clinical usefulness of *in vitro* drug-susceptibility tests.
5. The place for isoniazid blood concentration determinations as a guide to treatment.
6. The use of the secondary antituberculous drugs, such as cycloserine, pyrazinamide, viomycin, kanamycin, and thiocarbanidin.
7. The indications for the use of pyridoxine and the recommended dosages to be employed.
8. The indications for the use of corticosteroids and corticotropin.
9. The indications for, and timing of, pulmonary resection, surgical collapse procedures, and pneumotherapy during chemotherapy; and in this category of particular interest is the management of the so-called open-negative syndrome.
10. The usefulness of chemotherapy to prevent reactivation of inactive tuberculous foci in patients known to be at an increased risk, because of conditions such as pregnancy, diabetes, post-gastrectomy status, influenza, pneumonia, silicosis, et cetera.

So much for the controversial subjects related directly to chemotherapy, and now for the second part of today's topic. Under the heading "The Hospital and Home: Respective Roles in Tuberculosis Management," the following pertinent topics, unsettled topics, seem worthy of consideration.

In the first place, I believe some agreement should be established on definition of terms. The following terms which will be used in connection with this topic need not be formally defined, but I think each one of us should have a clear idea of what the panelist means when he uses them.

Under types of care given to unhospitalized patients we should distinguish between such terms as "clinic," "home," "ambulatory," "domiciliary," or "custodial."

Referring to types of patients and their attitude and behavior, we would like to know what is meant by a cooperative or an uncooperative patient, a recalcitrant patient, a public health menace, or a disciplinary problem.

When we discuss home conditions, we would like to know a little bit more than just the adjectives good, fair, or poor. And when we are discussing community facilities, such as hospitals, clinics, social and welfare services, and so on, we would like to know what is good, what is a fair facility, and what is a poor facility.

These are all important because of certain areas of disagreement which are related to the types of patients, facilities, and homes under question.

My second point is the relative importance of each of the following services to patients who are receiving effective chemotherapy in determining our attitudes toward hospitalization, and these should be, I think, debated among the panelists: the role of bed rest, rehabilitation, occupational therapy, health education, adequate nutrition, adequate housing, psychiatric care (particularly the care of alcoholics), and medical care for nontuberculous diseases.

Criteria or standards should be discussed relating to the following topics: hospital admission and hospital discharge, both for voluntary hospitalization and compulsory hospitalization; acceptance for treatment outside the hospital when hospital facilities are available and refused by the patient (there is a difference of opinion on this in some sections of the country); when should a patient receiving effective chemotherapy be considered noninfectious?; when should a tuberculous patient be allowed to return to work?; when should treatment outside the hospital be considered the treatment of choice for a tuberculous patient?; when should a patient with tuberculosis be treated without bacteriologic confirmation of the diagnosis?

A fourth category of problems is the advantages and disadvantages of managing tuberculous patients under each of the following conditions, and

this should elicit some differences of opinion: in a tuberculosis hospital; in a general hospital; by a clinic of a tuberculosis hospital; by a chest clinic of a general hospital; by a health department chest clinic; or by a private physician.

The management of tuberculous patients in communities with grossly inadequate hospital and clinic facilities is a real problem in an international symposium. Maybe we won't have time to go into that in too much detail, but certainly it should be listed here.

I think in this connection techniques of determining whether ambulatory patients are taking their drugs and techniques to encourage them to take them might be a topic worthy of consideration.

Then there are standards and principles to be used as guides in planning for future needs in tuberculosis management, a real need in communities which are now planning for the future.

It is probable that this afternoon's panel discussion will not only fail to give all the answers to the many questions raised, but may even bring forth a few which the introducer did not think of. It is to be hoped, however, that this discussion will at least lead to a clearer delineation of the many unsolved problems related to the management of tuberculosis and perhaps give us all better insight into the reasons for their existence.

DR. TUCKER: At this point, Dr. Chaves, I am not sure that I want to thank you! And I am also filled with envy, in the face of the distinguished performance by Panel One this morning, at the relatively finite field which that group had, compared to what Dr. Chaves has just outlined for this panel. I am saying this, Dr. McDermott, perhaps with a certain degree of envy simply because you have completed your task.

However, it is perfectly apparent that all of the topics to which Dr. Chaves has called attention are entirely valid. The purpose of this symposium, as I understand it, is to discuss just such matters and, to the extent that we have the opportunity this afternoon (and the members of the nuclear panel and the extended panels and others will bear with us), we will try to cover as much of the subject matter which Dr. Chaves has outlined as possible, but we make no promise at this time that we shall be able to cover all of it.

One of the nice parts of this Deborah Symposium is the rather integrated pattern of the six panels which has been outlined for us in the three days, and it is very natural indeed to move from the area of primary prophylaxis and secondary prophylaxis more immediately to the area of therapy, and to take up these problems of chemotherapy and the related problems of treatment in the home and in the hospital.

An immediate extension of some of the discussion in Panel One this morning, particularly that concerned with secondary prophylaxis, is: What are the indications for chemotherapy? The first part of the panel discussion this afternoon will necessarily need to be restricted to pulmonary tuberculosis for the time being—we shall broaden it perhaps a little bit later—and I should like to start out also by limiting our discussion in the panel to original treatment of pulmonary tuberculosis to get certain general principles out of the way, and then come back to necessary modifications of these general principles.

And so I am going to direct to Dr. Muschenheim our first question: Should tuberculous cases of doubtful activity be treated, including those treated successfully in the past, without antimicrobial therapy?

DR. MUSCHENHEIM: I presume, Dr. Tucker, that you are referring primarily to asymptomatic patients found in surveys in whom immediate assessment does not reveal that the disease is active or inactive.

DR. TUCKER: Yes, I am, Dr. Muschenheim; that is exactly right. How would you answer that?

DR. MUSCHENHEIM: I don't think that a categorical answer to that can be made at this time. As most of you know, I think, there have been hardly any actual comparative studies on this point. I have recently seen one report, however, in which this was done in nearly 200 patients equally divided between those receiving no therapy and those receiving isoniazid and PAS in conventional dosage. This study, I believe, was done in Edinburgh, with the usual difficulties about determining whether the patients actually were taking their drugs.

The roentgenographic deteriorations were not very different between the two groups, but it was determined, apparently to the satisfaction of the group studying these patients, that most of the deteriorations in the treated group occurred in those who had been determined not to have been taking their therapy. Corrected in this way there was a difference of, I think, in the neighborhood of 10 per cent as compared with 1 per cent

of deterioration. Roentgenographic improvements were in the neighborhood of 30 per cent in the treated and about half of that in the untreated. Eventual "positive" cultures were obtained in about 10 per cent of the untreated and I think in only one of the treated patients.

This, I think, certainly raised very definitely the practical question whether all such patients (providing one can be reasonably sure of the diagnosis) and possibly also patients known in the past to have been treated for tuberculosis without chemotherapy or perhaps with chemotherapy under conditions of short courses, whether it might not be desirable to pick these up now and treat them. Of course, this is something that involves quite a lot of practical difficulties.

DR. TUCKER: What is your personal preference, Dr. Muschenheim? You have been extremely impartial up to this point. Can you give us a little partiality?

DR. MUSCHENHEIM: I think that the principal problem really is one of diagnosis, as far as the patients found in surveys are concerned. Whether one treats them or not, they will need to be closely observed, and I would rather be inclined to wait until a positive culture or some other evidence is obtained that it is indeed a case of tuberculosis and that there is activity. I think that current therapy is so good that we need not be too hesitant to wait and observe the patient.

DR. TUCKER: Especially if the patient remains cooperative and continues to follow observation. Thank you, Dr. Muschenheim.

Dr. Badger, I am trying to think of a specific problem: An individual has been to a mobile chest X-ray truck, has had his X-ray taken, a suspicious shadow is seen, the tuberculin test is positive, we do not have bacteriologic confirmation. The chances are, in the judgment of an experienced clinician, that this is likely to be tuberculosis, but we have no way of knowing whether this is active tuberculosis or not.

What is your personal preference with regard to the treatment, the chemotherapy of this particular lesion in this patient?

DR. BADGER: So far as possible, I do think the diagnosis remains a very essential feature of whether or not you treat. It is actually my own practice to be sure that we are dealing with a positive tuberculin test, and I have become very reluctant to treat a patient who has no reaction to the tuberculin test; and under those circumstances prefer to look elsewhere for my diagnosis.

I think much can be gained by obtaining earlier X-ray films, and I think, as far as definitive diagnosis goes in the complicated problem, that perhaps we should not be entirely satisfied with one or two gastric studies of gastric contents. However, in many of the cases, I feel quite sure that the results are good enough to warrant bronchoscopic lavage and the production of positive results, which becomes increasingly great the more we see of it and practice it appropriately.

DR. TUCKER: No, it is not the intent here to go into a dissertation on the problems of diagnosis.

DR. BADGER: I don't plan to. I simply wanted to make it clear that the diagnosis should be established. Then, having taken all necessary diagnostic measures into account, the problem of whether this a lesion which should be treated or not may be decided.

DR. TUCKER: I take it that you have a good deal of caution in your own mind about treating a case of doubtful activity, in the absence of a positive diagnosis, even though you would suspect it to be tuberculosis.

DR. BADGER: I don't mind treating it particularly; I would rather be sure what I am treating, *but I would prefer to be sure that I am not treating the wrong disease.*

DR. TUCKER: Which is certainly understandable. But I am still trying, perhaps too hard, to press home a certain point. If you think, in the absence of proof that this is likely to be tuberculosis, and on the available evidence you are not sure of the activity of that presumed tuberculosis, do you favor immediate institution of chemotherapy?

DR. BADGER: I would favor initiating chemotherapy (and do it very frequently) after all the appropriate diagnostic procedures have been carried out.

DR. TUCKER: Have been initiated, at least.

DR. BADGER: And therapy itself may perhaps give you the clue to your diagnosis.

DR. TUCKER: Dr. Bignall, in England what is the approach to this particular problem?

DR. BIGNALL: I am not sure that I can really talk for England. I will say what I think. I agree actually with what has just been said. I have no hesitation myself in treating a patient rather than waiting to see whether the disease is active or not. In fact, I am not really sure how one tells whether it is active. However, I think it is fair to point out that the authors of the report mentioned by Dr. Muschenheim did make it

quite clear in their discussion that they were not recommending that treatment should be given to all patients merely on the results of this particular controlled trial. They made it clear that in their opinion (and with this I entirely agree) the decision to treat such patients was a matter for judgment in the individual case, and that this particular controlled trial might guide their choice of treatment or not, but it should certainly not determine it. I think, myself, that the characteristics of the individual in his work, whether one thinks he is likely to remain under close supervision, whether he is likely to take the drugs, and so on—all this would weigh very much more with me than the results of the controlled trial mentioned.

DR. TUCKER: Dr. Burke, without asking you to speak for ten provinces in Canada, would you care to say anything from north of the border?

DR. BURKE: We prefer to keep under supervision people who we believe have tuberculosis of uncertain activity. Our routine is to concentrate on trying to establish the status of the disease, using all means at our disposal.

I want to bring in for just a moment the laryngeal swab, which we think plays a part in the picture. We are fortunate in that we have public health nurses whom we can ask to go to the home to visit, and these nurses will do tuberculin tests on children, if any, in the home. Should we find a small child who is a tuberculin reactor, then we assume that a member of the household probably has active tuberculosis; partly for his sake and for public health reasons we then institute treatment.

DR. TUCKER: Here we have an interesting situation. This morning, in Dr. McDermott's panel, on the basis of theoretical considerations, as he was careful to emphasize, he asked for the opinions of the members of his panel, and the opinions indicated that in certain types of young persons, in particular, with positive tuberculin reactions but the absence of a demonstrable disease, the majority of the panel at least was in favor of chemotherapy.

At this panel we have a situation in which there is presumably more evidence of the presence of tuberculous disease, and there is a good deal of conservatism with regard to immediately instituting chemotherapy. I merely wish to point this out. Would anyone here take exception to this too broad generalization? (None) I guess they think I am still on the track.

I am a little surprised, frankly. Speaking as an internist and a clinician, I thought that we had already reached the point at which it was fairly common practice to have lowered the criteria, if you will, lowered the bars, changed our criteria for admission to therapy, in other words. It seemed that many of us over the years were seeing less disadvantage in chemotherapy of tuberculosis and more advantage relatively, and so were admitting to treatment on smaller indications. Dr. Chaves, as you see this problem from the standpoint of a person working not only in the City Health Department but in one of the hospitals of New York City, would you say that there has been a change in this direction?

DR. CHAVES: It is the practice of the clinics of the Bureau of Tuberculosis of New York City to assume (*1*) that the chest physicians are aware of the implications of a minimal lesion of unknown etiology on an X-ray and to institute all of the diagnostic procedures necessary to make a diagnosis; and, (*2*) that in the face of a positive tuberculin reaction, such a lesion of undetermined etiology, and possibly active, would be treated unequivocally and immediately without any hesitation whatsoever. That I think is what I would do personally if I had such a patient.

DR. TUCKER: I am not going to be able, even with the help of my associates, to settle this question, and so I am going to drop it at this point and perhaps some other panel of the symposium will take it up. I am now going to assume that the diagnosis of pulmonary tuberculosis has been established by whatever means have been suitable; that this is an individual patient who has not previously had chemotherapy; and to ask certain questions of members of the panel along these lines on the basis of such an assumpttion.

Dr. Robitzek, do you feel that it is always desirable to employ more than one drug for active pulmonary tuberculosis which has not been treated before?

DR. ROBITZEK: I can answer that very briefly: yes, sir.

DR. TUCKER: Always desirable to have more than one?

DR. ROBITZEK: Indeed I do. Let us go back for a moment. I presume that your question is based on the premise of the original-treatment case which is a pulmonary one, if I read this

correctly—the manner in which the questioning is going from the first question to the second, which implies that this is a pulmonary case—I don't want to get into the question of pleural effusions, and so on.

DR. TUCKER: Not at the present.

DR. ROBITZEK: Given a pulmonary tuberculous lesion shown to be active, the question of therapy arises. It seems to me that it has been amply established and certainly has been my own experience that the use of two drugs is basic.

DR. TUCKER: Dr. Burke, how would you answer this question?

DR. BURKE: If the patient has open pulmonary tuberculosis, two drugs.

DR. TUCKER: By "open" do you mean sputum positive?

DR. BURKE: Sputum positive, yes. If the patient doesn't have open tuberculosis, we occasionally use one drug alone.

DR. TUCKER: Dr. Davies?

DR. DAVIES: I would tend to agree with Dr. Burke. I think, given a 70-year-old man who has had a gastric resection and has a minimal lesion, with no evidence of cavity, it would be ridiculous to give that man two drugs. I think he should be treated with isoniazid alone. However, for the great majority of patients, I would prefer two drugs.

DR. TUCKER: Dr. Bignall?

DR. BIGNALL: Coming from England I think the answer is probably self-evident. I would certainly use more than one drug, but I don't like generalizations that apply or that are intended to apply all over the world in all circumstances. I can only say that in the particular circumstances at home, in the United Kingdom, I think that two drugs are desirable. It may be very different in circumstances in which economic pressures are quite different.

DR. TUCKER: Dr. Badger?

DR. BADGER: I would make the additional exception that I think those persons who may be susceptible to one drug or the other may be forced to take a single drug. I don't think it worth while to press PAS to the point of extraordinary gastrointestinal problems. In patients who cannot take PAS, if you are warranted in using two drugs (as in open cavitary disease), I certainly would not hesitate to shift to streptomycin. It seems that this problem really continues from this morning's discussion, and that we are dealing here with the noncavitary versus the cavitary problem. I think we feel very differently about the noncavitary, the mildly disseminated nodular-appearing disease on X-ray, in which these patients do just about as well on one drug as they do on two.

DR. ROBITZEK: Early this year I saw a 75-year-old gentleman and, using the philosophy mentioned a moment ago, I treated him with one drug, and I have lived to regret it. This patient, whose disease was clearly tuberculous but not open and active at that time, became positive some time during the summer, and now I am forced to give him double-drug therapy and I regret that I didn't right at the beginning.

DR. TUCKER: That I hope will be much more of an exception than the rule in such circumstances, but even one exception of that sort must be taken into account.

Without completing this poll of the panel, I am now, however, going to say that even though this sounds as though there were some disagreement, as Dr. Badger has just indicated, there probably is much more agreement than would appear, namely, that most clinicians and others are convinced that for the open case, as Dr. Burke put it, the one which is cavernous or in which the sputum is definitely positive—the tubercle bacilli are multiplying rapidly—it is generally advisable to use more than one antituberculous drug concurrently.

On the other hand, there may be special circumstances in which the use of one drug alone may be indicated. With this introduction I should like to ask Dr. Muschenheim whether he believes that there is not a place for the use of a single drug, particularly isoniazid. May I ask you, Dr. Muschenheim, to tell us what you think the indications for single-drug therapy with isoniazid may be?

DR. MUSCHENHEIM: I think we are getting into what Dr. Canetti has called a theologic discussion in respect to whether or not one should always use two drugs or whether one may sometimes use single-drug therapy. This morning I was beginning to think that the very idea of single-drug therapy had emerged from the category of sheer heresy because two-drug therapy for the secondary prophylactic treatment was not even mentioned. I do find myself in disagreement with the majority of the panel with respect even to pulmonary tuberculosis inasmuch as there are really some quite adequate studies indicating

that in minimal tuberculosis, for instance, and in moderately advanced tuberculosis in which there are at least no demonstrable cavities, no difference has been shown in the results comparing isoniazid alone and isoniazid with a companion drug.

Therefore, it seems to me that it would be well to bear in mind that there is a general principle that the simpler therapy can be, the better; and I have been particularly impressed recently in respect to the most popular companion drug to isoniazid, namely, PAS, that there are an increasing number of published reports with respect to not mere intolerance to PAS but actually to dangerous and fatal reactions. Indeed, I think there have been as many deaths from PAS reported as there have been from pyrazinamide, for instance; and we have practically abandoned pyrazinamide, except for very special indications, because of its toxicity.

Not only this, but I think it is quite generally recognized that a hypersensitivity reaction to PAS by some mechanism that is not understood can provoke a hypersensitivity reaction to isoniazid or streptomycin when these are given concurrently. I think all of us have encountered instances in which we could not give either isoniazid or PAS because of a hypersensitivity reaction.

Scientifically it is difficult to prove or to demonstrate that PAS is the primary and principal offender in this link-type of sensitivity reactions. It is true, however, that hypersensitivity reactions to isoniazid when given alone are extremely rare and that hypersensitivity reactions of the particular type that I refer to as very dangerous ones, including hepatitis and encephalopathy, and so forth, are known to occur with PAS when given with streptomycin or when given alone. I think these reactions have never been observed with either isoniazid or streptomycin unless these were accompanied by PAS.

I am quite aware that in open cavitary tuberculosis comparative trials do indicate some advantages in two-drug therapy. Nevertheless, these advantages are really not very great and I think that, before one makes a general rule based on a few percentage points of difference, one should bear in mind the very real disadvantages that may ensue from adding a second drug, and in instances in which it cannot be demonstrated even that there are such advantages, it seems to me that double-drug therapy is almost indefensible.

Dr. Tucker: Dr. Muschenheim, if I have understood you correctly, you are saying that the disadvantages of multiple-drug therapy must be weighed or balanced against the advantages; and, in general, the more extensive and advanced the disease, the more the advantages of two- or three-drug therapy outweigh the disadvantages. At the other end of the spectrum of pulmonary tuberculosis, the more minimal the extent, the more the disadvantages of multiple-drug therapy outweigh the advantages. Would this be a fair summary of your position?

Dr. Muschenheim: Yes, I think that is exactly it.

Dr. Tucker: To come back to my question of a few moments ago, you probably would favor single-drug therapy with isoniazid in the relatively small minimal lesion, the one in which, if bacteriologic confirmation has been obtained at all, it has been obtained with considerable difficulty; in other words, that the lesion is discharging relatively few tubercle bacilli; and you feel that single-drug therapy is suitable.

Then, of course, there is another related situation: After a case has been treated which is definitely open and strongly "positive" and has "converted" and the cavities are closed, would you not also feel that there was a place for single-drug therapy for a continuation period, therapy with isoniazid alone?

Dr. Muschenheim: Yes, I do think so very definitely, and I think that this is perhaps one of the most important clinical things to determine; and that is, in cases in which multiple-drug therapy is an advantage at the beginning, for how long is it an advantage? I very seriously doubt that it is of any advantage at all after the so-called target point has been reached.

Dr. Tucker: We are unfortunately not going to be able to develop all the points on which Dr. Muschenheim has touched; in fact, he has given us an extremely good perspective on the whole problem of chemotherapy in his remarks.

I think that the way to summarize up to this point would be that, even though there is disagreement among specialists, among experts in this field, there is an increasing body of sentiment that some of the earlier impressions, that it is always desirable to use two drugs instead of one, are being re-evaluated. There is a greater degree of recognition at present than previously that under certain circumstances (and these circumstances can be of a wide variety, as have here

been indicated) it is entirely permissible and, indeed, quite proper, to consider single-drug therapy, especially with isoniazid. I know that this rather general statement will not meet with the detailed approval of all members of the panels, but unless there is a serious challenge I am going to leave this particular subject—single-drug therapy with isoniazid—at this point. Do I hear a serious challenge?

Dr. D'Esopo, we're delighted to have you with us.

DR. D'ESOPO: I would like to come to the defense of PAS briefly. What Dr. Muschenheim said is true, that PAS is a very frequent sensitizer and has been the cause of some deaths, and so forth. But I am quite sure that all of these are preventable. I think the serious and fatal reactions to PAS are due to physicians' having overlooked the earlier manifestations. I have followed this point very closely in our own cases and in the literature, and I don't think anyone has anything to fear from PAS if the cases are watched closely. We use so many dangerous drugs these days that hypersensitization to any drug is one of the prime concerns of physicians, Just because PAS is a frequent sensitizer I think is really nothing against its use.

DR. TUCKER: In other words, you are taking advantage of this opportunity to point out that, even though there are some unfavorable reactions both along toxicity and hypersensitivity lines, if we keep watching this closely and manipulating the drug therapy, we can overcome many of these disadvantages. At this point does anyone care to say whether we are in a position to discard PAS as a companion drug to isoniazid in favor of some other drug to use or to recommend the use of it routinely? Do I hear a volunteer?

DR. MUSCHENHEIM: I would like to put it in the form of a question because I don't really know what the most recent results are in patients treated with isoniazid and cycloserine in relatively low dosage or in higher dosage covered by pyridoxine, but I would think that, if the toxicity experience has in fact been as low as it promised to be a year or so ago, this would certainly be a much more desirable companion than PAS.

DR. BADGER: I just want to say a brief word on the other side of the question: that I am surprised that Dr. Muschenheim has had trouble with PAS. To me PAS very rarely has a highly allergic and sensitivity reaction associated with it—high fever, nausea, vomiting, temperature of 104°F. It's a "rare bird" and you don't see it very often. Even though it does occur, the patient can almost always be desensitized by stopping PAS for three weeks and then starting in again with minuscule doses and increasing the dosage over a period of time.

I think that the gastrointestinal symptoms that we see are not hypersensitivity reactions, but are probably irritative, much like those with large doses of aspirin; and the patients are, almost all of them in my experience, able to be carried very easily on very small doses. Nobody has yet told us that a smaller dose of PAS may not be just as effective as 12 grams a day. Personally, if they can take 4 grams or 6 grams, it is okay with me so long as they are free from symptoms.

DR. MUSCHENHEIM: May I make just a brief comment, Mr. Chairman? I am not talking of my experience because I avoid PAS as much as I can, but in the last six months we have had three patients in the hospital, including one of my patients to whom I did give PAS, with extremely severe hypersensitivity reactions and of the type to which I alluded before. I don't think that the occurrence is necessarily preventable. I would agree with Dr. D'Esopo that, if one is very alert, one may appreciate that a febrile reaction in a patient getting PAS is due to this: but there are a lot of people on PAS who have febrile illnesses and nobody stops the PAS. It can simulate infectious mononucleosis, hepatitis from other causes; and, as I indicated earlier, there is a cumulating literature on this subject. There are a good many cases reported.

DR. TUCKER: I think Dr. Robson would like to make a comment.

DR. ROBSON: Experimentally the combination of one of the thioureas, 1906, with isoniazid gives very good results indeed.

DR. TUCKER: Is that thiocarbanidin?

DR. ROBSON: No, it is a related compound. We have also tested thiocarbanidin, and, on the whole, this thiourea gives better results than thiocarbanidin. It is certainly experimentally more effective (and I must limit myself to experimental results) than the combination of isoniazid with PAS. I have been surprised that such a combination hasn't been used clinically. I know there are some historical reasons for it, but we know that 1906 can be safely given to man because of its use in leprosy; and I, again

basing my opinion entirely on the experimental results, would suggest that such a combination deserves definite clinical investigation.

DR. TUCKER: Actually there have been some clinical studies with which I am familiar, though on a very small scale. I think, however, we are not going to be able to take the time to go into this difficult and highly complex question of other drugs which may be companion drugs to isoniazid to too great an extent.

If I may attempt to summarize: There are many different possibilities, some of which have been investigated to differing degrees; so far none has yet come through the preliminary evaluations in sufficiently impressive strength to seriously challenge the place which PAS has won up to the present. But also it is equally obvious, as more and more reports of serious reactions to PAS are coming to the surface, that it will be highly desirable to continue this type of investigation.

As has also been mentioned, we have so far neglected (and I am afraid we are going to continue to neglect) the problems of dosage. Another question related to PAS which has recently been published from the Mayo Clinic in Rochester, Minnesota, is whether or not a single dose of PAS a day, as Dr. Karlson and Dr. Carr have shown in their work, may not possibly have a place and overcome some of the disadvantages. However, I am going to go on to some other aspects of two- or three-drug therapy, and I am going to ask Dr. Davies: Do you believe that there is any one regimen which is preferable for the initial treatment for most or all cases of pulmonary tuberculosis?

DR. DAVIES: I am sorry you asked me that question —

DR. TUCKER: I'll be glad to ask someone else if you wish.

DR. DAVIES: That is a question I would like to ask rather than to answer. I don't know that there is any single regimen that is desirable for almost all patients.

DR. TUCKER: I am not going to ask Dr. Muschenheim that question because I know his answer will be no. I am going to try to see if anyone thinks he knows what is the one regimen. I am going to call on the extended panel down here. Dr. Raleigh, do you know of any one regimen which is preferable for initial treatment of most cases of pulmonary tuberculosis?

DR. RALEIGH: No, I do not.

DR. TUCKER: Is Dr. D'Arcy Hart here? (Not present)

Dr. D'Esopo, how would you answer that question?

DR. D'ESOPO: I think there is no choice really. I think they are equally good.

DR. TUCKER: About equally good. *You* didn't say "about" — *I* did.

DR. D'ESOPO: The usual three combinations of two drugs; I think there is very little to chose from among them.

DR. TUCKER: I think the general impression so far is that careful evaluation in cooperative studies and the experience of many other persons in the use of the best known two-drug combinations of the three principal drugs, isoniazid, streptomycin, and PAS, indicate that the therapeutic and toxicologic differences between them is not of very large magnitude. From that standpoint, there is not much difference though, if sufficiently large numbers and sufficiently detailed analyses are made, there are certain differences.

DR. ROBITZEK: Might I just throw in a little dissenting note? I think it is quite true that you can't tell the difference between two and three drugs over a short period.

DR. TUCKER: I'm sorry. I was now speaking of the question of differences between three two-drug regimens, not between two and three drugs. But please go ahead and talk on that if you like.

DR. ROBITZEK: It seems to me that you will see some difference based a little bit on your preliminary evaluation of the patient when you see him. I think that sometimes you can anticipate that you are faced with a prolonged period of therapy in order to achieve the target point. For this reason I think, at least on theoretic grounds which have stood up reasonably well in our hands, that it is desirable to limit your regimen to the simplest possible combination, anticipating that one day you are going to be required to go on to other regimens. The aim is to provide a useful drug or combination of drugs to a susceptible organism for as long a period of time as possible rather than as heavily as possible over a short period.

DR. TUCKER: We have now just talked more or less in the abstract about differences between drug regimens and have taken into little account characteristics of the patient or of the patient's disease.

Dr. Muschenheim, in your opinion should the

selection of such a regimen be determined entirely on general grounds or should the extent and character of the disease be taken into account, or any other factor which you can think of? For example, does it make any difference whether the selection of drugs is made for hospital treatment or home treatment?

DR. MUSCHENHEIM: Yes, I think it makes a great deal of difference based on the type of disease, the general characteristics of the patient (particularly age), and I think it depends also on other circumstances. I think the principal thing, of course, to be determined is the type of patient and the type of disease. I personally prefer not to give streptomycin to elderly patients, and I think this is an opinion also shared by many. Elderly patients are more susceptible to the toxic potentialities of streptomycin, so that in an elderly patient with cavitary disease in whom I think there may be an advantage in two-drug therapy, I would prefer to use isoniazid and PAS. Certainly in patients with extremely acute disease and in the most serious forms, such as miliary and meningeal tuberculosis, I would certainly think that isoniazid with daily streptomycin represents the best of the standard regimens available.

I think also, coming back to this question of isoniazid alone as it may relate to special circumstances, that there is no very great disadvantage even in the cavitary case in using isoniazid alone. We studied a series, which we reported last winter —

DR. TUCKER: Dr. Muschenheim, I thought we had passed that subject by.

DR. MUSCHENHEIM: It was a small series, to be sure, in which isoniazid was used as the initial therapy in unselected moderately and far advanced cases, and additional therapy was introduced later on only when necessary; and this worked out quite satisfactorily. So that in situations, for instance, those in which there are not facilities for hospital care or for close supervision, I think it is infinitely better to start treatment with isoniazid alone than with a two-drug regimen during the preliminary phase before the patients can be hospitalized; I think one loses very little and takes very few risks.

DR. TUCKER: I am going to turn now to problems of dosage just in two respects. One could talk a long time about the infinite variety of dosages of the different drugs which are available. One which we shall consider will be high-dosage isoniazid, by which I mean 10 milligrams per kilogram or more of body weight (just by definition for the sake of argument), versus lower dosages; and the other will be daily versus twice a week, or intermittent, streptomycin therapy in a two- or three-drug combination.

Dr. D'Esopo, from your experience, do you believe that high-dosage isoniazid plus daily streptomycin is a regimen that almost never fails to achieve sputum conversion?

DR. D'ESOPO: I don't know anything about high dosage of isoniazid. I think it is worth investigating.

DR. TUCKER: Dr. Davies, how would you answer that question?

DR. DAVIES: Given a patient with severe disease and a rather poor prognosis, I would feel better if he began treatment with daily streptomycin and isoniazid. I think that some evidence, which to me is not conclusive, has been presented that isoniazid ought to be at high dosage levels, and it seems to me that this is a matter that rather urgently warrants study with a randomized and rather large series, preferably limited to patients with far advanced disease and bilateral cavities.

DR. TUCKER: There is a certain degree of caution in that, but I think it is sound, Dr. Davies.

Now let's break this down. That was almost too difficult a question. It is my impression, from talking with many of my friends who are working in and are interested in this field with respect to the question of high-dosage isoniazid versus low-dosage isoniazid, that there is fairly general agreement that only in a relatively small percentage of patients with original-treatment tuberculosis does it really make any difference, but the advocates of high isoniazid dosage are fairly strong in their belief that it is important to detect this small percentage and to give high isoniazid dosage.

This clearly is related to the whole question of the rapid acetylation and inactivation of isoniazid, and this in turn is related to the competitive acetylation with PAS and similar agents; and we cannot go into this in detail. But is there agreement—and I shall ask just this simple question of several individuals—that this problem of the importance of high isoniazid dosage is probably limited to a relatively small percentage of patients with active pulmonary tuberculosis?

Dr. Badger?

DR. BADGER: Yes.

DR. TUCKER: Dr. Robitzek?

DR. ROBITZEK: Yes, sir, I agree.

DR. TUCKER: Dr. Muschenheim?

DR. MUSCHENHEIM: Yes.

DR. TUCKER: Dr. Chaves?

DR. CHAVES: Yes. I don't have too much experience. Our problem is to get patients to take any isoniazid.

DR. TUCKER: Dr. Bignall, have you had some experience?

DR. BIGNALL: I have had no experience at all in high isoniazid treatment. In fact, at home I think it is pretty true to say that we always use 200 milligrams in two doses of 100 milligrams twice a day; but, of course, I have spent a week in Denver since I came to the States!

DR. TUCKER: Dr. Burke, do you feel that it applies only to a relatively small number of patients?

DR. BURKE: On the basis of our observations, yes, to only a handful.

DR. TUCKER: Dr. Davies?

DR. DAVIES: Yes, sir.

DR. TUCKER: Is there a challenge to this from anyone in the audience?

DR. RALEIGH: I think it is quite true that the advantage of the additional dosage of isoniazid applies only to a small fraction of patients treated, but I don't think that the relationship between this and the metabolic rate of the isoniazid in individual patients has been demonstrated at all. It hasn't in any controlled series, and I think that conclusions are being jumped at wildly from insufficient data.

DR. TUCKER: May we attempt an agreement at this point along the lines that Dr. D'Esopo indicated, that it is sufficiently intriguing and there is enough information presented to point out the clear necessity for further extensive investigation of this particular problem. And, of course, this is under way in many institutions.

With that, with your permission I am going to leave the question of high isoniazid dosage—and I realize there will be a certain degree of disappointment that we have not spent more time on it—and turn equally briefly to the question of daily versus twice-weekly streptomycin.

Now, to narrow the area of this equally large potential discussion, let us assume that the patient is not really elderly; let us say that he is not over fifty-five years of age. Let us say that he has advanced disease, that it is desirable to use two-drug therapy, and that the determination has been made to use isoniazid and streptomycin. This is an original-treatment patient with large cavities. We want to do the very best we possibly can with this individual. Is it permissible to use the streptomycin on an intermittent twice-a-week basis or is it preferable in nearly all instances to use it on a daily basis at least for the first few months of therapy?

I hope I have narrowed this down quite a bit, and I am going to call first on Dr. D'Esopo to answer this question.

DR. D'ESOPO: If I remember correctly, our own cooperative studies and the British Medical Research Council studies have both shown that there is a higher percentage of isoniazid resistance when streptomycin is used twice a week. I think on this basis that daily dosages of streptomycin are preferable. However, I can't recall any data which show superior clinical efficacy, that is, in terms of conversion of sputum or cavity closure.

In our own hospital, where we are prejudiced in this respect at least, we use daily streptomycin with isoniazid and find very little toxicity from daily streptomycin. This is my own personal preference. Except for the emergence of isoniazid-resistant organisms, I am not so sure that there are any data showing the superiority of daily streptomycin.

DR. TUCKER: Dr. McDermott, would you care to speak to this point?

DR. MCDERMOTT: I think that wherever it is possible to give the streptomycin twice a week, it is usually possible (although not invariably possible) to give it daily, and I think without question it should be given daily. Certainly John Crofton's experiences in Edinburgh and the Dressler-Russell-Middlebrook experiences with patients in Denver, as well as experiences in animals, show very clearly that the results are most spectacular when this is done.

It also seems to me that there is a theoretic consideration here that is of great importance, and that is that there is nothing sacred about the number 2 in talking about two-drug regimens. It is two *particular drugs* that are important; that is, it is a question of how do two particular drugs work in a situation. I think your own reports from the Veterans Administration, Dr. Tucker, have shown quite convincingly that it doesn't much matter what the companion drug to isoniazid is so long as it is given daily. It is the *daily* business that is important. It is the fact that the organisms under the influence of

one drug are being affected by the other drug. I think without question one should give the streptomycin daily instead of twice a week.

May I add one thing, Dr. Tucker, and that is that, as the record stands, the panel is on record as saying that of the three drugs, streptomycin, isoniazid, and PAS, it makes no difference which two-drug regimen you use. That means that the panel is taking the position that streptomycin–PAS (and in the U. S. streptomycin–PAS is streptomycin twice a week), streptomycin twice a week and daily PAS, are the equivalent of daily streptomycin and isoniazid.

DR. TUCKER: Thank you, Dr. McDermott, for pointing out what could easily be a misimpression and, therefore, to backtrack just a moment: Cooperative studies in at least two countries (and it may be more) have clearly demonstrated that the combination of intermittent streptomycin and daily PAS is not as effective, in open tuberculosis particularly, as either of two two-drug combinations containing isoniazid. This is what I think needs to be clarified.

Just to elaborate a point which Dr. D'Esopo made with regard to daily and intermittent streptomycin with daily isoniazid, I hope I am correct in remembering that in the British Medical Research Council trials (and, Dr. Bignall, you will correct me if I am wrong), they compared daily streptomycin and daily isoniazid with daily isoniazid and daily PAS, and found the combination of daily isoniazid and streptomycin slightly superior therapeutically.

In this country, in the Veterans Administration–Armed Forces Cooperative Study, we compared daily isoniazid and daily PAS with daily isoniazid and twice-a-week streptomycin, and found the latter not quite as good. I know of no direct comparison of intermittent streptomycin versus daily streptomycin, but I think, if we may use this common regimen of daily isoniazid and daily PAS, that between the British studies and the Veterans Administration–Armed Forces studies in this country we can conclude that, in addition to the point of higher rate of isoniazid resistance, the combination of streptomycin twice a week with daily isoniazid is not quite as effective as that with daily streptomycin. This is aside from questions of toxicity.

DR. BIGNALL: Could I just correct you there? I think I am right that the British Medical Research Council did in fact make a direct comparison between streptomycin daily and isoniazid daily and streptomycin intermittently and isoniazid daily, and found a very clear and substantial difference in what we believe to be the only thing that really matters, that is, the emergence of resistant strains in the sputum.

DR. TUCKER: Thank you. It is entirely appropriate for this panel also, if only briefly, to refer to the question of duration of therapy because this will be indispensible in talking about the relative roles of home and hospital, even though this is a part of the discussion of tomorrow morning's panel.

I am going to try and restrict the discussion of this in the following manner. I am going to ask the question: Do you feel that there is any place in original-treatment tuberculosis for therapy under one year's duration under any circumstances for active proved tuberculosis?

Dr. Badger?

DR. BADGER: Excluding those situations that arose this morning, I think we are dealing now with clinically active proved tuberculosis, original treatment. I believe there is little or no reason for giving less than a full year of chemotherapy in any proved active case of tuberculosis.

DR. TUCKER: Does any member of the panel wish to disagree with Dr. Badger on this? Apparently not.

Dr. Badger, again, do you feel that the duration of chemotherapy should be related to the extent of the disease more primarily, or do you feel that it should be related more primarily to the response of the disease to the particular regimen?

DR. BADGER: I think both of those should be taken into consideration; but, on the whole, it is the response to chemotherapy which I consider most important and which should be the really guiding feature. Certainly the more advanced cases of tuberculosis do require longer therapy to attain a degree of stability and to reach the so-called target point. I think we recognize that two years is probably better than one in the tougher cases and, in those that are still tougher but doing well, even much longer than two years is advisable.

DR. TUCKER: Dr. Robitzek, what are your views about the duration of therapy? Do you feel that you have a very objective criterion as to when you feel it is safe to discontinue chemotherapy?

DR. ROBITZEK: I have no basic disagreement

with Dr. Badger at all. I think he stated it better than I could. Perhaps I would like to emphasize a little bit more the response to therapy. I think it is urgent to continue therapy for a longer period of time in an individual who hasn't perhaps responded as promptly as we think clinically he should have, irrespective of the extent of the disease. I think this is possibly a factor that should be weighted just a little bit more.

DR. TUCKER: I think this is included here only as a necessary preliminary to talking a little later in this panel about certain aspects of home care, and I hope very much that tomorrow's panel will be able to develop the theme more fully. I may add only that some statistical analyses of the results of differing durations of chemotherapy in original treatment tuberculosis would seem to indicate that, as the total interval of chemotherapy is increased, the difference in results by successive increments of duration of therapy gets smaller and smaller. In other words, twelve months is much better than eight months; eighteen months is somewhat better but less good than twelve months; two years is a little bit better than eighteen months, but just a little bit; and so on. The increment of improvement gets smaller with each increment of duration of therapy.

Now, this is not completely solid, but there is some suggestive evidence along this line. This, of course, means that the tougher cases respond less and less well after that much therapy.

There is one other aspect to this, and here I am not even going to ask questions unless someone wishes to speak. The Public Health Service in this country did some very beautiful studies on deliberately changing chemotherapy from one *ab initio* to another at a given period of time without any specific clinical indication for change. If I may attempt to summarize that briefly, it was to the effect that a change from a non-isoniazid-containing regimen to an isoniazid-containing regimen was superior to not changing to that isoniazid-containing regimen; whereas, a change from an isoniazid-containing regimen to a non-isoniazid-containing regimen offered no advantage over continuing on the original chemotherapy.

This is of some importance and I believe that it would be very desirable if there were other investigations of deliberately planned changes of chemotherapy during original therapy, as well as re-treatment therapy for that matter. Does anyone care to speak to this point?

DR. MCDERMOTT: As I recall, there was some planning in that these were failures on Regimen A.

DR. TUCKER: I thought not.

DR. MCDERMOTT: I thought it was the one-third who were failures and were still infectious on Regimen A who were switched to Regimen B.

DR. TUCKER: Is Dr. Carroll Palmer here? I saw him this morning. (Not present)

DR. DAVIES: I think that is correct. The switch was on treatment failures, and by random choice half of them were switched and half of them were not.

DR. TUCKER: I am glad to be corrected.

DR. TUCKER: Dr. Badger, may there be a place for continuing isoniazid therapy alone after the completion of conventional regimens of two or more drugs of over two years' duration? I believe you have had some 25 or more cases which you have kept under treatment with isoniazid alone for very long periods.

DR. BADGER: That is quite true. I cannot speak from having correlated the details of the series as yet and can only comment concerning those patients who have been continued on isoniazid alone for one to four years after the completion of conventional regimens of drugs. In the latter cases, my regimens may be longer than conventional elsewhere. It has been my custom to continue dual-drug therapy for twelve to twenty-four months in minimal and moderately advanced, noncavitary disease and for two to three years, or longer occasionally, in far advanced and cavitary disease. Continued use of isoniazid alone in patients *after* completion of these regimens has been based upon various factors: refusal of surgical treatment, unsuitability for surgical treatment, a family history of tuberculosis, evidence of relapse before starting drugs, the intention of raising a family, old fibrotic cavitary disease persistently "negative," advanced disease that has done well with multiple drugs, diabetics, and those with silicotic disease or extensive exposure to silicotic dusts. So far, none of the patients on long-continued isoniazid alone have relapsed bacteriologically or by X-ray. Much more time is needed, however, for proper evaluation and follow-up.

DR. TUCKER: Dr. Davies?

DR. DAVIES: I wonder if I could say a word about that. It seems to me that is most important, because I hear people say very frequently

that of course you can't keep up isoniazid forever; and, if you keep it up for six years, I suppose you could keep it up for sixty years. I think maybe you can keep it up forever and that that is the proper indication for some people at the present state of our knowledge.

DR. TUCKER: "Indefinitely prolonged" is one phrase in the literature.

Another part of this problem, of course, is what has already been referred to as the "open-negative," which means the persistence by X-ray criteria of what has been interpreted as a tuberculous cavity in the face of persistently negative bacteriologic results, including sputum cultures and cultures of gastric lavage contents. The only difference in what has been bandied about a good deal as to the criteria for the definition of the open negative has been the duration of status as just now defined. This is of some importance because it is my impression, at least, that when such an individual has been negative bacteriologically for only a relatively short period of time, measured in terms of four to six months, there is a definite relapse rate; but, when the duration of bacteriologic negativity has exceeded one year, there is an increasing amount of evidence that the relapse rate is much, much lower.

If I remember figures correctly, the relapse rate for the former group (in which negativity for purposes of definition is around six months) is approximately 20 per cent whereas, if negative for over a year, the relapse rate is, let us say, 5 per cent or less.

These are not well-established data, but at least there is something here to go on. I will ask certain people whether they feel that for the open-negative case—and for purposes of this question I shall arbitrarily say negative bacteriologically for at least one year—there is a different criterion for the duration of chemotherapy.

Dr. Davies?

DR. DAVIES: Without any statistical evidence and really because of the lack of statistical evidence, I like to continue isoniazid, at least, on "open-negatives" indefinitely, and by indefinitely I mean until evidence is forthcoming that this is not necessary.

DR. TUCKER: In other words, you are recognizing the special situation largely reflecting our ignorance in late results and, therefore, are hedging, as it were, for the future.

Dr. Badger, do you feel that this "open-negative"—negative bacteriologically for at least a year—has a different indication for the duration of chemotherapy?

DR. BADGER: It has, in my own experience. I think you have identified open-negative with the duration of time attached to it, which I think is particularly important. This also applies to the group of patients who have complicating troubles like diabetes, intercurrent pulmonary infections that are frequent, a patient who may have pulmonary fibrosis of nontuberculous origin, or patients who are going through a variety of crises. Certainly one feels a good deal of security (at least I do) in the utilization of isoniazid over a long period of time. This includes treatment of the cavitary case which is at the present time "negative" or was "negative" when isoniazid alone was continued.

DR. TUCKER: This question of the open-negative may come up again tomorrow in the problem of relapse. I am sure that it will be discussed and, hoping that it will be, I shall pass on from that subject to another, possibly equally controversial. This is the role of corticosteroid therapy in the management of pulmonary tuberculosis.

To introduce this particular aspect of the discussion I should like to say that it is my impression that there is thoroughly general agreement now that, in the case of the acutely ill patient with tuberculosis, the toxic individual (particularly when the expected response to standard chemotherapy is still somewhat uncertain), there is more and more a tendency rather routinely to employ corticosteroid therapy.

Fortunately, the availability of less toxic corticosteroid products has permitted their use without complications to a greater extent than just a few years ago. Furthermore, I think it has been established that there are fewer complications from the standpoint of dissemination of the tuberculous infection in face of such management when the chemotherapeutic coverage is adequate by present-day standards.

Is there any disagreement with this very general statement that I have just made, namely, that it is now quite appropriate and, in fact, even advantageous to consider using corticosteroids in the management of the acutely ill tuberculous patient when one may expect some difficulty in the management without these agents?

DR. BADGER: I would put in my nickel's worth of disagreement in this only because I come from

an area where corticosteroids are perhaps handled with a little bit more conservatism.

DR. TUCKER: Is this the Harvard influence, Dr. Thorn's influence?

DR. BADGER: No, that of Dr. Kass and Dr. Finland and a few others. I think I would like to interject the thought that I don't think we yet know the answer to this problem. I am not opposed to the use of corticosteroids; I am not enthusiastic for their use. But I do not believe that enough controlled double-blind studies have been done with and without corticosteroids to really be sure.

I think we are perhaps inclined to draw generalized conclusions from the observation of a single case, but I think that the observation of a single case works on both sides. I remain extremely skeptical still, but am willing to be convinced; but I see the dangers of corticosteroids so widely apparent that I think that these are drugs which should be used after more knowledge has been obtained. I only say that I don't know. I think they should be tried, but they should be carefully tried under most careful and astute supervision.

DR. TUCKER: I am, frankly, surprised. I didn't know Boston was still so conservative.

Dr. Robitzek, do you feel that there is more of an opportunity to employ the corticosteroids more freely in the treatment of seriously ill tuberculous patients?

DR. ROBITZEK: This is an interesting question to raise for me because Dr. Muschenheim took me to task on a panel last June in New York for stating that I saw relatively little use for the corticosteroids except in instances in which there were allergies to some of the drugs. Of course, that rather opened my eyes and I have looked a lot more closely at our clinical material at Sea View Hospital in the subsequent months.

In spite of this perhaps more discerning search, I still have not seen much indication for it in the patients that come to Sea View Hospital. Conceivably they are not now as acutely ill as they used to be, because they may have been screened at another hospital before they come to us, but it has always been fairly standard at Sea View that we have clinical patients who are most acutely ill; and I am just not convinced that, under good, sound antimicrobial therapy, having a susceptible organism and an effective drug, the corticosteroids provide any great advantage. This may have to be reversed if I ever see that one case; but to date I haven't actually seen it.

DR. TUCKER: Dr. Muschenheim?

DR. MUSCHENHEIM: I think that this is a problem in which the controlled trial is virtually impossible. For one thing, it is very difficult to define the patients or to select the patients which would fit the category in which I think a good many careful observers are quite convinced that adrenocorticosteroid therapy may literally be life saving. But, of course, one can't really say when a patient is moribund until after the patient has died. For this very reason those particular patients on whom one would wish to use it, if one feels there is evidence of its value, are the ones on whom on ethical grounds one would not wish to do a control study.

I certainly do not think that the indications are frequent in pulmonary tuberculosis for the use of adrenocorticosteroids, but I do think there have been several series reported in some detail, and I have personally observed some patients with actually fulminating tuberculosis with severe prostration, with hypertonia, patients who might reasonably not be expected to survive, who have become dramatically better with the use of the hormone supplementation.

Indeed, I have seen not only this. I have seen patients who have been treated with what I think anyone would accept as a maximal chemotherapeutic regimen, namely, high-dose isoniazid with daily streptomycin, actually respond so poorly and have the disease visibly progress over a period of weeks to such an extent that one might think that one was dealing with a drug-resistant infection. Not only does the use of the hormone produce a very rapid clinical improvement, but also a very rapid objective improvement of a disease process which was going the other way. I think this is an area in which there is no substitute for clinical impressions.

DR. TUCKER: Touché! I take it then, Dr. Muschenheim, that you reserve the addition of corticosteroids in the management of tuberculosis for very special circumstances in rather grave emergencies; is that correct?

DR. MUSCHENHEIM: Yes.

DR. TUCKER: Dr. Badger, would you agree with that, too?

DR. BADGER: I would think so, yes; only I would still say that I don't know yet what effect they really have and I think they have not yet

been adequately studied by any means at all. We see the reverse happen so often that I still believe that this is an area for study and an area for more controlled observation which cannot be carried out very well only in individual cases.

DR. TUCKER: Dr. D'Esopo, from your experience with the use of corticosteroids, in a moment or two could you give us your remommendations either for use of the corticosteroids or for further studies in this direction?

DR. D'ESOPO: I can't say anything about indications. I don't think we know enough about them. In our experience with these agents, patients improve very rapidly and there are rapid changes in X-rays which I conceive to reflect the resolution of non-necrotic types of inflammation.

The most important area of study, I think, is the effect on cavities, and there we have seen something very interesting that suggests that steroids enhance the sloughing of cavities and tend to convert tuberculous cavities to a sort of pneumatocele, that is, an air space, without any pathologic evidence of tuberculosis in some cases. This I think is the most promising line of investigation.

DR. TUCKER: Have you seen any serious disadvantage to the employment of corticosteroids with adequate chemotherapy coverage?

DR. D'ESOPO: We have been very fortunate in having had none of the things we all dread, hemorrhage, and so forth. Our most serious toxic effect was a psychosis.

DR. TUCKER: It is my impression that we do not yet have enough evidence to recommend as a panel or as a group of individuals a great increase in the use of corticosteroids in the management of tuberculosis at the present time. I believe that it is safe to say that there is enough evidence now on the basis largely of individual studies and careful impressions that it is a relatively safe procedure to employ them when there is an indication for them. Therefore, there should be further studies on a more carefully controlled basis as to what the contribution of this particular class of agents should be.

If it is permissible, I will pass on with that brief summary of this particular subject to the next subject (and it will necessarily have to be very brief), that is, the infinitely complex problem of the management of re-treatment pulmonary tuberculosis as contrasted with the management of original-treatment pulmonary tuberculosis.

For purposes of definition, by "re-treatment tuberculosis" I mean when there has been an original course of chemotherapy which has been discontinued for at least one month and then subsequently there has arisen, for any reason, a need for resumption of chemotherapy. This means, then, one course of chemotherapy of whatever duration, a definite discontinuation of it, an interval of at least one month, and then resumption, though not necessarily of the same regimen. This is so complex, and there are so many combinations and permutations into which we shall not go, that I am going to ask only one very difficult question, and I trust that the persons to whom I will address the question will be as concise as they can be.

Assuming that a patient with active tuberculosis and with organisms exhibiting resistance to high concentrations *in vitro* of isoniazid, streptomycin, and PAS—in other words, complete resistance, shall I say, to all three of the major drugs—what is your favorite regimen for chemotherapy?

Dr. Bignall?

DR. BIGNALL: I don't like the adjective "favorite" because, having a relatively small tuberculosis practice, I luckily haven't seen a very large number of these cases. I will answer very briefly with what I use rather than with what is a favorite one. I use viomycin and tetracycline.

DR. TUCKER: Dr. Chaves?

DR. CHAVES: At present in a clinic population we would use isoniazid in the standard dosage, 5 milligrams per kilogram of body weight.

DR. TUCKER: In the face of a high degree of *in vitro* resistance to isoniazid?

DR. CHAVES: I did not forget that. We would use, I repeat, isoniazid, 5 milligrams per kilogram, and cycloserine, 500 to 750 milligrams.

DR. TUCKER: For those not familiar with cycloserine dosage, this is a lower dose of cycloserine than has been employed, but is one which is within the range of safety from the standpoint of toxicity.

Dr. Badger, how would you answer this question?

DR. BADGER: I think you have already pointed out that it is one of the toughest knots we have to untie. My own inclination and my own practice is this. On a re-treatment case there is a period of time before you have any idea whether

or not the organisms are resistant to drugs. During that period of time I would restart the patient on the conventional therapy that he may have been on before and would continue it (if I thought the dosage inadequate) in larger dosage because we do know that many of those who are recorded as being resistant really are not.

In the second place, I think it is very difficult to give full credence to susceptibility tests as usually carried out on solid media, and I am a little bit inclined to go ahead with conventional therapy again, perhaps in equal or larger doses, until the clinical response is observed. If it is good, the chances are that the susceptibility studies would have led you astray. By that means you have in reserve the other drugs which may be useful when you are really hard put to it for surgical treatment or for other types of treatment.

DR. TUCKER: Dr. Robitzek—faced with triple resistance?

DR. ROBITZEK: I think there has to be a clear differentiation between laboratory resistance and clinical resistance.

DR. TUCKER: *In vitro* resistance, I am speaking of.

DR. ROBITZEK: With *in vitro* resistance I would certainly prefer, if I could, to have the offending area resected. If not, I should go along with Dr. Chaves' approach with cycloserine and isoniazid precisely as he would and in approximately the same doses, in spite of isoniazid resistance.

I think, however, we should differentiate a little bit here whether or not this is an individual whose therapy was stopped and who had then secondarily broke down, or an individual who continued under therapy and broke down. In the first instance, it is possible that he might indeed have susceptibility retained, in which case I would prefer to go back to the original regimen. If, on the other hand, the subject were under therapy when he broke down, then I would prefer to go to the second approach which is surgery, if it can be done, for the many reasons that will come up in other panels; and, if not, I would prefer cycloserine and isoniazid as my second choice.

DR. TUCKER: So there is a certain common theme here that we are not too convinced of the significance of the standard *in vitro* tests of susceptibility and resistance, particularly in the case of isoniazid; that there is a tendency to add, nevertheless, other drugs. In the case of Dr. Bignall, he mentioned viomycin in combination with tetracycline. In the case of two other panelists, they have mentioned cycloserine as a drug which they have found useful. There is a certain degree of agreement here.

Now, Dr. Muschenheim, faced with triple-drug resistance and the need for chemotherapy, what is your preferred course of action?

DR. MUSCHENHEIM: This is a question that I dislike to answer briefly.

DR. TUCKER: I am going to have to ask you to do so if you possibly can.

DR. MUSCHENHEIM: I do think that the really important point that emerges here is that one should not necessarily be guided completely by the *in vitro* susceptibility tests; but, even more particularly, I agree entirely with those who have indicated they would continue isoniazid. I think that with very high degrees of *in vitro* resistance to streptomycin, repeated on several observations, there probably is not very much use going on with streptomycin. Quite emphatically, I think virtually all of these patients should continue to receive isoniazid or should receive it again, and the reason I said I don't think this is a question that can most desirably be answered briefly is because I think this opens up the whole question of the significance of isoniazid resistance, which I know now is not the time to get into.

With respect to other drugs, if the clinical situation indicated that the streptomycin and PAS resistance figures really were significant, I would turn to cycloserine and probably viomycin. In other words, I would be guided by the compatibility of the drugs from the toxicity standpoint and give the patient everything I could.

DR. TUCKER: Would anyone here care to refer to kanamycin, one of the newest antibiotics?

Dr. Muschenheim?

DR. MUSCHENHEIM: I have had no experience with it.

DR. TUCKER: Dr. Julia Jones?

DR. JONES: I think the present situation regarding kanamycin is that it is necessary to find out whether the nontoxic dose will be clinically effective, and whether the drug will protect other drugs against emergence of resistance. This information is not yet complete, largely because the series of cases which have been studied and more or less completed were bankrupt patients

as far as drugs were concerned, with types of disease that could not be estimated in terms of clinical response.

But I believe not only from our experience, but also from that of other groups who had a similar experience, that ototoxicity is a very serious problem at the dosages used.

DR. TUCKER: Is this not somewhat comparable to the situation with respect to viomycin some seven or eight years ago, when there was considerable renal and ototoxicity on daily doses or fairly high dosage, and then later it was found that the dosage could be modified downward to an acceptable level?

DR. JONES: I think this is correct, but I don't think we now know whether it will be effective at that dose.

DR. TUCKER: Dr. Steenken, from the experimental standpoint is there anything in your animal work which would help us with this problem of re-treatment in a patient faced with the knowledge of *in vitro* resistance to the three major drugs? Have you any clues which might be helpful to clinicians?

DR. STEENKEN: From the experimental standpoint I would say no, because we have not been able to create a host in which we can get consistently resistant organisms to deal with. In order to test these drug regimens experimentally, there would have to be a host in which chronic disease permitting emergence of resistant organisms could be produced.

DR. TUCKER: So there isn't anything sufficiently comparable to the problems of chronic pulmonary tuberculosis from your experimental work to help too much?

DR. STEENKEN: No, not unless you used many, many monkeys and many, many rabbits and had a selected group that had open cavitary disease in which the organism became resistant.

DR. TUCKER: Dr. Schmidt, would you care to say anything at this point from your work with simian tuberculosis?

DR. SCHMIDT: I am afraid I can't add anything to the mechanisms of control, but I think that Dr. Steenken is a little bit in error. I cannot add anything as to the effectiveness of changing drug therapy or continuing on drug therapy, but I would like to point out that the mechanisms for studying this problem are at hand in the cavitary disease that one gets in the monkey. It is not a very difficult thing with inadequate drug treatment to end up with cavities in 100 per cent of the survivors. Some of them are not fortunate enough to survive. So this is a problem which is quite susceptible to attack.

DR. TUCKER: You have just recently developed a model which may make it possible to get some information in the monkey along this particular line.

DR. SCHMIDT: Dr. Tucker, I think we are confusing two things here. In unsuccessfully treated simian tuberculosis, the presence of cavities containing resistant organisms is a common finding: streptomycin-resistant and isoniazid-resistant organisms, and so on. In addition, we have been able to obtain chronic cavitary disease by partially immunizing monkeys, and these are the previously untreated animals. This provides us with an opportunity to see what the liabilities are of developing resistance and the difficulties of treating primarily cavitary disease.

DR. TUCKER: I think this is a tremendous step forward in the experimental work, Dr. Schmidt, and I hope that it will be possible—although I realize how difficult it is for you to encompass all the studies that you would like to make—to get some information from your laboratory which will help us on this particular point.

At this relatively late hour I am going to turn to the fascinating subject of the relative roles of home and hospital. Much that has occurred in the past hour and a half has been preliminary to this, and to get right into this now I am going to ask Dr. Burke, first, whether he thinks hospitalization is an essential part of the treatment of all forms of active tuberculosis.

DR. BURKE: I do not think that hospitalization is an essential part of the treatment of all forms of tuberculosis. I like as far as I can to divide the patients into their categories, decide who has active and open tuberculosis, who has active and closed tuberculosis, assess the patient, assess his home; and in a certain number of cases I think it is perfectly reasonable to treat people with tuberculosis in their homes. In other cases, it is obviously very much better to send them to an institution.

DR. TUCKER: Well, Dr. Burke, how would you define the patient whom you regard as suitable for treatment to be initiated and carried on entirely in the home?

DR. BURKE: In general, he is a person with minimal tuberculosis and closed disease as far as we can determine.

DR. TUCKER: Would you take into account at

all the socio-economic factors, the cooperativeness of the patient?

DR. BURKE: Indeed I would. I meant assessment of lesions, assessment of patient, assessment of his immediate environment.

DR. TUCKER: You would feel, then, if I understand you correctly, that with more minimal disease, in the patient with noncavitary pulmonary tuberculosis who is not likely to have too difficult a home environment, it might be entirely suitable to have his treatment initiated and continued in the home?

DR. BURKE: Yes, except that I would like to say it should be a patient who has a good home environment, not a too difficult one.

DR. TUCKER: Dr. Robitzek, what are your criteria for the patient for whom it is appropriate to initiate and continue the therapy of active tuberculosis in the home?

DR. ROBITZEK: Well, sir, I always ask myself the question: Does the hospital provide something, or will it provide something, that the patient cannot get at home? Of course, if the answer is in the affirmative, obviously he is a hospital candidate. This would apply, of course, to acute toxic situations in which there might be a nursing care problem, and it would certainly apply in situations in which for cultural or social reasons, i.e., in a society in which people are crowded together, this individual is a menace in the household, and in a sense this is restating what Dr. Burke has just said.

Generally speaking, if he is an original treatment case the chances of getting treatment started and completed in the home are usually pretty good. If he is a re-treatment patient, and particularly if he has a bad social background, he practically demands hospitalization—and I almost said incarceration.

DR. TUCKER: Dr. Badger?

DR. BADGER: I think it is possible to reproduce most of the hospital situations at home under all of these circumstances if you are put to it. I actually prefer, and find it very much easier and simpler, to have a patient begin his treatment in the home, where all of the things that have been spoken of can be taken care of easily and his own indoctrination can perhaps be carried out a little bit more simply. All the problems of handling infectiousness can be carried out at home provided the patient has a room of his own, and I don't think they need to be a source of worry provided the patient is cooperative.

One thing that I have found important is whether the family is willing to have the patient at home and willing to do the things which we think are necessary until the stage of infectiousness is passed. This is not always easy to work out, and a patient who is resistant to hospital care may also be resistant to home care. So there are many, many intangible factors in the situation, but I am very sure that with a cooperative patient on original drug treatment it can be worked out eventually for the patient to do as well at home in all probability as in the hospital.

DR. TUCKER: Dr. Bignall, would you care to speak to this point?

DR. BIGNALL: Yes. I agree with practically all that has been said, but I don't think it is quite such a simple question as was posed because there are other things to be considered. When you say treatment at home, you presumably mean the same sort of treatment that would be carried out in the hospital, rest and so on. The other point to be decided, of course, is whether rest is necessary. I know this is going on to another thing, but it is very difficult to answer the question as posed. I should add that I very much prefer to treat patients at home than in the hospital. I don't like hospitals.

DR. TUCKER: Dr. Davies, I will, nevertheless, persist for a moment and ask you how you would define the patient who in your opinion is suitable for treatment to be initiated and carried on entirely at home.

DR. DAVIES: I think I would agree with most everything that has been said. I would like to add one more item to the criteria for choosing the patient, that is, that he have an intelligent and cooperative doctor as well as an intelligent and cooperative patient. Perhaps that is even more important.

A point that interests me in this subject is how many of these people there are, and I suppose that varies a good deal with one's practice and with the area in which one lives. It would be my guess that, in Florida, perhaps 5 per cent at the least and 10 per cent at the most of all of the people who develop active tuberculosis might do well on treatment carried out entirely at home. I would be interested in the estimates of other members of the panel as to how that percentage runs in their communities.

DR. TUCKER: I will run down the list and take them in a straight line down the table.

To repeat the question: In your experience,

Dr. Burke, of all the patients coming to your attention in need of treatment for active tuberculosis, what percentage may suitably be treated in the home, what percentage approximately?

DR. BURKE: I don't know quite how to answer that. We had 300 people with tuberculosis under supervision in the year 1957. Approximately half of them had disease which we considered of questionable activity. The remaining 150 had disease of about one-third minimal and the remainder moderate to far advanced. I would estimate that we treated one-half of the minimal cases (that would be about 30 patients of 50 who had minimal disease) in their own homes.

DR. TUCKER: That is a very thorough answer.

Dr. Bignall, what would your answer be?

DR. BIGNALL: A guess. I think probably two in every three.

DR. TUCKER: Dr. Chaves, do you have any insight from your clinic or other activity?

DR. CHAVES: It is not too clear just what criteria are being used for this percentage, but I will give you one anyway. It is in the neighborhood of what was given by Dr. Davies. He said 5 to 10 per cent. I would say that is pretty close to what I would guess.

DR. TUCKER: Dr. Badger?

DR. BADGER: You are all familiar with the Public Health Service studies. In Massachusetts a year ago Dr. Weidman surveyed this problem and just under 50 per cent of patients with active tuberculosis were being taken care of at home. Now, it is a little hard to be sure exactly how many of those were primary treatment cases. The reason why it is hard to be sure is because Dr. Weidman also asked a good many of the practitioners across the state how often they reported their cases of active tuberculosis and they said, "Well, Dr. Weidman, you know how it is. We're busy. We don't always have a chance to report them, but we're taking care of them just the same." So I don't really know how many there are and I couldn't quote a figure, but I know that that figure is very high.

DR. TUCKER: You haven't answered my question.

DR. BADGER: Yes, I did. I said 50 per cent of active tuberculosis cases were being cared for at home.

DR. TUCKER: Of the patients coming to your attention for treatment, what percentage, roughly do you consider suitable for treatment entirely at home?

DR. BADGER: You mean of my own patients who come to me? I can't answer that, but with minimal tuberculosis I would guess (that is, minimal tuberculosis, noncavitary) that probably 50 per cent of them are now being taken care of at home because our Channing Home closed a short time ago and I have no place to send them. So, if they don't want to go to the state institution, I take care of them at home, and I take care of many more than I would otherwise; so that is not an entirely fair answer for me to give.

DR. TUCKER: We'll let you off the hook with that.

Dr. Robitzek?

DR. ROBITZEK: Excluding the patients who would go to Dr. Chaves' Health Department clinic, who for financial and cultural reasons can't afford private care—and this represents certainly a good deal more than half of the total patients in the New York City area where I practice—I would say that of the residual patients certainly 80 or 90 per cent of them at least are suitable for home treatment.

DR. TUCKER: We have quite a range of percentages, gentlemen. Dr. Muschenheim, do you care to come in between or cap it at either end?

DR. MUSCHENHEIM: I have no idea.

DR. BURKE: I was speaking exclusively of original treatment cases, not of the re-treatment cases. That is another story. And now that I have the microphone I would like to say that I think every re-treatment case should be admitted to the hospital and reassessed.

DR. TUCKER: Would there be disagreement with this latest statement of Dr. Burke?

DR. CHAVES: Yes, I would disagree. Again, it is a general statement, and there are situations in which a working man who has had tuberculosis successfully treated in the past has on a routine X-ray showed up with a little minimal lesion. He has been off his drugs for six months or so. I see no harm in re-starting him on his original regimen which brought him to a stable point and in observing him right after that. I would say that is an exception to what Dr. Burke says.

DR. BURKE: I would say we probably had missed a cavity, or something, in the original treatment.

DR. TUCKER: It is perfectly clear that there is a wide range in practice in advising patients, and in evaluating the need of patients, to have the original treatment of their tuberculosis initiated

in the hospital or at home. Probably we started this discussion off on the wrong foot. Perhaps the place to have started it would have been to ask this question: Is there any evidence that hospital treatment is, in fact, superior to home treatment for the average tuberculous patient?

Dr. Davies, how would you answer that question?

DR. DAVIES: If you speak about evidence from rigidly controlled studies on randomized patients, I do not know of any such evidence as that. I think there are some studies that show some suggestive evidence that for the average patient hospital treatment gives better results. However, I think that Dr. Chaves, and perhaps other members of the panel, are more familiar with those studies and could quote them better than I can.

There is one point I would like to make, and that is that we do not know for sure why people get sick with tuberculosis. I think we do know that it is not simply a matter of infection because most of the people that get infected do not get sick. There are some other items, and those items vary. A person infected with tubercle bacilli may stay well for many years and then get sick. Apparently something has changed. For want of more precise information, maybe we can say that he gets sick because of some stress of one kind or another added to his infection. In that case we can assume usually, I believe, that that stress is going to be associated with his environment at home or at work or both. Perhaps by hospitalizing that patient we may not only get him to take drugs, and so forth, but we may (at least temporarily, while we are getting control of the situation) eliminate that stress to which he has been subjected.

DR. TUCKER: It is very difficult, of course, to compare home and hospital treatment because the total environment differs so radically, and there are so many components of each which are not comparable. However, we have here had one element, one variable, referred to repeatedly and that is the variable of bed rest.

Dr. Bignall, in what type of case do you think that bed rest is essential? In what type of case do you think bed rest may be harmful?

DR. BIGNALL: The first question is a relatively easy one to answer. It is essential, I feel, in any person who is clinically ill; by that I mean is feeling unwell, has fever, has lost weight, and so on. In other words, it is the same sort of criteria that one would use in advising rest for any other infectious disease.

The second question is a very difficult one to answer; it's almost a catch question. I think bed rest can be harmful in some cases, but it doesn't depend on the lesions. I think it depends on the person's character, his personality. In my experience, I feel I have done harm to some patients by getting them into the hospital and trying to keep them in the hospital. This is, I think, far too difficult a question to be answered concisely.

DR. TUCKER: Fair enough, Dr. Bignall. Of course, what I was thinking of was that before we had effective chemotherapy, twelve or more years ago, most of us believed firmly that rather rigid bed rest was most conducive to recovery from tuberculosis. At the same time, many of us recognized that there was an element of harm for the patient from some standpoints. Now the question is whether enough of a contribution from bed rest might still be pertinent today in the presence of very effective chemotherapy so that this possible benefit of bed rest might still need to be considered in the face of the recognized disadvantages.

If I may attempt to answer this question myself, I would say that for the average patient with tuberculosis, the not acutely ill patient, let me say, it seems to me that the disadvantages of bed rest outweigh the advantages; or, if we disregard disadvantages, that the advantages of bed rest, the contributions of bed rest, are relatively small compared with those of chemotherapy. I have sometimes likened the contributions of bed rest to a small letter "a" and the contributions of chemotherapy to a large letter "B." Theoretically, if "a" and "B" each has a positive contribution, then the sum of "a" plus "B" should be greater than either "a" or "B"; but this, obviously, depends on the relative size of the "a" and the "B" and thus I think of bed rest as a relatively small "a" and chemotherapy as a relatively large "B." I think, therefore, that the positive contribution of bed rest is relatively small when added to that of chemotherapeutic agents.

I don't know what the extent is to which there would be disagreement with this point of view. It is quite possible that there are those here that would care to speak on the subject even at this late hour.

DR. DAVIES: I would not like to exactly

disagree, but it does seem to me that we have not yet any adequate studies to show that bed rest does not have something to add in the case of the patient with extensive bilateral cavitation. I believe that this is the only patient for whom bed rest may have something to add, and that the value of this addition has neither been proved nor disproved, and it is worth studying.

DR. TUCKER: I would not quarrel with that, Dr. Davies.

I want to turn now to some other aspects of this problem of home and hospital, and ask those of the panel, particularly those who have had experience with this matter of home treatment—by which I mean primarily treatment outside of the hospital *ab initio* and continued—what may be the principal problems of attempting to manage active pulmonary tuberculosis entirely outside the hospital.

Dr. Chaves?

DR. CHAVES: I think the principal problem that we have encountered is the fact that we cannot be sure that the patients are taking the drugs that we are giving them. If we could be sure of that, we would then have other problems, but this one is so overwhelmingly the first problem that I don't think there is any point in going into any of the others.

DR. TUCKER: In your experience, Dr. Chaves, would you say that the probability of gross irregularity in the taking of drugs is low, moderately high, very high—in some round terms like these?

DR. CHAVES: I would say 2½ plus; I would say it is moderately high.

DR. TUCKER: Would you say it would probably apply to more than half the patients then?

DR. CHAVES: I would say in the case of PAS it applies to 50 per cent or more of the patients. With isoniazid I don't know, but I would guess in the neighborhood of 15 to 20 per cent.

DR. TUCKER: Dr. Badger, in your experience in the management of patients outside the hospital, do you find this gross irregularity in the taking of drugs a serious problem?

DR. BADGER: No, I do not find it a very serious problem. With the indoctrination of my patients I find that they get in touch with me very promptly if they have difficulty taking their drugs at home and they confess sooner or later that they have or have not. I must say that with me personally it is not a serious problem.

DR. TUCKER: Dr. Robitzek?

DR. ROBITZEK: That has, roughly, been my experience, as outlined by Dr. Badger just now. This hasn't been a very serious matter. I think there are a couple of other problems, though. I state one because I don't entirely agree with the question of rest and its having been set aside to such a limited proportion in the total picture of therapy. I think that the analogy to closure of cavity sometimes is like a broken leg with a compound fracture and infection. You can give enough penicillin to clean up the infection, but you still have to immobilize the leg in order to get the bone to heal in proper position.

A cavity is a mechanical thing and you can sterilize it perhaps, but I think there are times when, in order to get closure, you have to have some immobilization. I have repeated examples of patients who did not rest during the early days of therapy; and when they did the cavities closed. Perhaps bed rest is a small "a" but it is still an "a" in the total picture.

The third feature which I think is a problem is the feature of alcoholism in the unsupervised patient at home. This is such a recurring problem that we handle it with some regularity in any new patient whom we see. This is mitigated a little bit by the fact that I think I can do a better job of psychotherapy in my office or in the patient's home than I can in the hospital, so perhaps the two things equalize each other a little bit. I can give more time, more attention, and can better understand the social and other problems, and perhaps be more helpful with them, in an individual who is in my office or at his home than I can in the hospital where I have to divide up my time among large numbers of patients. Nevertheless, the question of alcoholism is one so chronically recurrent that I don't think it can be overlooked.

DR. TUCKER: Dr. Muschenheim, what are the problems that you encounter?

DR. MUSCHENHEIM: I think it is largely a matter of the social and economic status and the patient's intelligence. I think in our economically lower segments of the population there are these difficulties. In the economically better-off segment I think there are no difficulties, and that the question of hospitalization should be based entirely on whether special procedures, either diagnostic or treatment procedures, are needed.

DR. TUCKER: I think it is clear from this brief rundown on the problems encountered in the management of active tuberculosis outside the

hospital that a great deal depends upon the character of the patient, the disease, the personality and capacity of the patient to cooperate with management; and, as someone said earlier, certainly the skill of the physician is involved also. I think it is also apparent, though it has not been very clearly specified, that there is a considerable capacity adequately to manage patients with active tuberculosis outside the hospital, assuming that the conditions are sufficiently favorable. But this is the trouble, the nugget of the problem: that that is a very large assumption.

What I have not asked anyone, and shall not, but leave for the future to determine, is whether, with this assumption of adequacy of home environment, we can really do without as large a number of beds for tuberculosis as we have had in the past. Perhaps this will come up in Panel Six on Saturday afternoon when Dr. Cooper and his panel will be taking a look into the future.

Dr. Muschenheim, I do want to ask just one quick question in this connection: Do you think that the "open-negative" patient, the one who has been negative for a year specifically, is safe to mingle with his family in home management?

Dr. Muschenheim: Yes, I do, if that patient is under supervision and continuing on therapy.

Dr. Tucker: We have not touched upon forms of extrapulmonary tuberculosis. There is one of them which is rather different from almost any other form of extrapulmonary tuberculosis, and this is so-called idiopathic pleural effusion which for purposes of this brief discussion I shall relabel tuberculous pleural effusion. In some respects this is quite different, principally because it is much closer to the primary tuberculous infection than pulmonary, skeletal, or renal tuberculosis, for example; and in some important respects the management of tuberculous pleurisy with effusion differs from that of pulmonary tuberculosis.

I want to give Dr. Burke, who has been a close student of this particular problem, just a few moments to tell us if he would care to, in what way he thinks it is important to manage the patient with this tuberculous manifestation differently from the patient with pulmonary tuberculosis.

Dr. Burke: Thank you very much, Mr. Chairman. First of all, I would like to start off with this challenge. I think that people who have tuberculous pleurisy with effusion should be admitted to the hospital and should be given strict bed rest for several months on end; this in addition to antituberculous drugs. My reasons for this are simply these, that from experimental studies we know that rapid and deep breathing hurry tubercle bacilli out of the pleural space into certain lymph nodes and on to the bloodstream. We know that rest, on the contrary, tends to keep the tubercle bacilli in the pleural exudate and reduces the chances of transport to the parasternal and the para-aortic nodes, and now you all will know that I am talking about carrying on into the bloodstream.

The result is that we are making a very special effort to persuade general practitioners in our area to admit patients with tuberculous pleurisy with effusion, or so-called idiopathic pleural effusions, to tuberculosis hospitals for investigation and close study as well as treatment.

I think that sums it up pretty well. I might just add this, that I wouldn't be surprised but what we would find that rapid and deep breathing may have some effect, too, on the transport of tubercle bacilli from alveoli to the regional lymph nodes of the lung. However, that we don't know yet, and it is high time that we learned all we can about it.

Dr. Tucker: Thank you very much, Dr. Burke, for sharing with us some of the results of your very fascinating studies.

Ladies and gentlemen, the hour has grown late. With your kind tolerance I have deliberately gone overtime because, as I indicated, the subject matter assigned to this panel was so very large; but, the hour being late, I shall not attempt—as Dr. McDermott did so well this morning—to recapitulate or to summarize. There have been too many diverse subjects. Rather, as we have gone along I have attempted brief summaries on different aspects of this problem.

The only possible over-all brief summary that one could give is to repeat what Dr. Chaves pointed out in his excellent introduction: There is much more unknown and controversial in these areas than is known and noncontroversial.

Thank you.

PANEL THREE

Panel members, left to right: Israel Epstein, Oscar Auerbach, Seymour Froman, Gardner Middlebrook, John D. Steele, William Steenken, Jr., M. J. Robson, James W. Raleigh, F. Ronald Edwards

PANEL THREE

THE PROBLEM OF RELAPSE OF TUBERCULOUS LESIONS UNDER CHEMOTHERAPY AND FOLLOWING TREATMENT; THE DURATION OF DRUG TREATMENT; THE PATHOLOGY OF HEALING TUBERCULOUS LESIONS; BACTERIOLOGIC PROBLEMS

Chairman: GARDNER MIDDLEBROOK
Introducer: JOHN D. STEELE
Panelists: OSCAR AUERBACH
F. RONALD EDWARDS
ISRAEL EPSTEIN
SEYMOUR FROMAN
JAMES W. RALEIGH
J. M. ROBSON
WILLIAM STEENKEN, JR.

DR. MIDDLEBROOK: Ladies and gentlemen, let us begin the third session of this symposium. The topic is an even more formidable one than those which were considered yesterday. It really includes those which are listed: the problem of relapse of tuberculosis under chemotherapy and following treatment; problems of the duration of drug treatment, which were touched upon yesterday; problems of pathology of what might be considered "healing" tuberculous lesions; and bacteriologic problems.

Dr. Middlebrook introduced the members of the panel:

Dr. F. Ronald Edwards—Mr. F. Ronald Edwards in British custom—Lecturer in Thoracic Surgery, Chief of the Department of Thoracic Surgery at the University of Liverpool, Senior Thoracic Surgeon of the Liverpool Regional Hospital Board and United Liverpool Hospitals, England.

Dr. James W. Raleigh, Secretary of the Committee on the Chemotherapy of Tuberculosis of the Veterans Administration of the United States.

Dr. J. M. Robson, Professor of Pharmacology at the University of London and Guy's Hospital Medical School.

Dr. William Steenken, Jr., Director of the Trudeau Laboratory and the Trudeau School of Tuberculosis.

Dr. Seymour Froman, Medical Microbiologist at the Olive View Sanatorium, and Research Microbiologist at the Medical School of the University of California at Los Angeles.

Dr. Israel George Epstein, Associate Professor of Medicine at New York Medical College, and Director of Pulmonary Diseases at Metropolitan and Bird S. Coler hospitals in New York.

Dr. Oscar Auerbach, Associate Professor of Pathology at New York Medical College, and Chief of the Laboratory Service at the Veterans Administration Hospital at East Orange, New Jersey.

The Chairman, Dr. Gardner Middlebrook, is Director of Research of the National Jewish Hospital at Denver; Associate Professor of Microbiology, University of Colorado School of Medicine.

Dr. Steele will introduce the subject.

DR. STEELE: While the problem of relapse of tuberculous lesions under chemotherapy and following treatment is important to the internist, it is of equal importance to the surgeon because in many instances the risk of surgery must be balanced against the risk of relapse. Possibly that is why I have been given the responsibility of introducing this subject, and not because, as one of my friends suggested, I have had more relapses in my practice than most other people! The rate of relapse is complicated by many factors which must be taken into consideration in evaluating any retrospective follow-up study and in the planning of prospective follow-up studies.

Definitions are of the utmost importance. For instance, when should observation begin and when should it end? When should patients be observed in relation to the duration of chemotherapy? How can we accurately define the type and character of disease without resorting to extensive jury reviews? Are we to base our classification of the severity of the disease on the numbers and sizes of cavities at the beginning of treatment, or should we reckon as well on the response to treatment?

How can we take into consideration the nature of the lesion at the start of chemotherapy as far as its pathologic components and history are concerned? Shouldn't we be able to correlate

bacteriologic and roentgenographic findings more satisfactorily than we do at present?

It seems to me that these are factors which are, unfortunately, disregarded frequently in evaluating tuberculosis therapy, obviously because their classification becomes so complex.

How can we compare modern relapse rates with those which are fairly well documented for the prechemotherapy era? In addition to the chemotherapy variable, haven't our bacteriologic and roentgenographic methods improved so much in the past fifteen years that cases formerly classified as good therapeutic results would now obviously be considered unsatisfactory?

Also, our classifications have changed so that we cannot go back into the literature and make valid comparisons with the old relapse rates. I suspect that a considerable number of the old "arrested" and "apparently arrested" cases would actually have been found to be active by more accurate modern methods of evaluation, and vice versa; many of our present "drug inactives" with large caseous foci may actually be active.

Can the microbiologists help us to predict relapse? Does the finding of viable tubercle bacilli in a resected lesion even after long-term chemotherapy mean that this patient's chances of relapse are greater than when viable tubercle bacilli are not present?

Have we reached an end point as far as the accuracy of our laboratory methods is concerned, or are we going to have to say fifteen years hence that any comparison of 1958 and 1973 relapse rates would be completely valueless?

We could always use a more accurate bacteriologic determination to differentiate a truly negative sputum from a "drug-negative" sputum. Will an accurate serologic test for activity be available soon?

Is the character of healing or attempted healing of tuberculous lesions going to change again in the next fifteen years? What effects can we expect, for instance, from an increased use of the steroids or of a new potent antituberculous drug? Will we still be discussing open-negative and residual closed lesions fifteen years hence?

Ten or fifteen years ago we considered that the relapse rate after five years of apparent arrest was relatively low. Now where is our safety zone? Is it five years after chemotherapy has been discontinued, or is it five years after reaching an inactive status regardless of administration of drugs?

Does the length of hospitalization have any bearing on relapse rates? Should not all studies of relapse take into consideration sociologic, psychologic, and emotional factors? Many tuberculosis hospitals are receiving more patients from penal institutions and more alcoholics than a few years ago.

What about duration of chemotherapy? I believe that the tendency has been to increase the length of chemotherapy courses because clinicians have been afraid to stop drugs when patients were doing well. Possibly these same clinicians have gained impressions from their experiences with relapses.

In our own hospital, with slightly over four hundred beds for tuberculosis, during the past year we have gained the impression that relapse rates are increasing. We have a little book in which we note the most obvious instances of relapse in patients who are on, or have recently been taken off, apparently adequate courses of chemotherapy. Twenty-six cases have been entered in this little book in the past three months.

Finally, has long-term antituberculous chemotherapy actually been used for a long enough period so that we have some indication, at least, of relapse rates following treatment, or must we confine our efforts to developing precise long-range studies to obtain our answer?

Mr. Chairman, I hope that the members of this panel can answer at least a few of the questions which I have posed.

DR. MIDDLEBROOK: I had a purpose in not introducing Dr. Steele, but letting him start right-off. He is one of the two members of the panel who are surgeons and, if one examines the backgrounds of the other members of our nuclear panel, without regard to the orbital group before us, I think it is quite clear that we have here a team of experts who represent the various disciplines which meet in actual practice to consider the problems of treatment of tuberculosis, not original treatment of tuberculosis but treatment of patients who present what is ill-defined, but which we call relapse for lack of a better term.

We could start this right-off by discussing definitions and trying to get each member of the panel to define what he means by relapse. There is only one aspect of this definition which I think we should establish rather clearly for ourselves and for our audience before we continue. When we speak of relapse, do we mean relapse during the

first five or six months of chemotherapy, or do we mean relapse after this period?

Yesterday's second session did not consider problems of drug treatment failure or its mechanisms. Great confidence was placed on the effectiveness of antimicrobial therapy. It seems to me that today our problem is to define somewhat the limitations of the effectiveness of antimicrobial therapy or adjuvant therapy and to establish some conceptual integration of the various modalities of treatment. This might permit us to decrease the real incidence of what might be called primary relapse, on the one hand, and secondary relapse, on the other.

Would it be acceptable to you, Mr. Edwards, to define relapse at these two different levels and use the term "primary" and the term "secondary" in this fashion: primary, some time during the course of chemotherapy after the patient is termed bacteriologically negative, he becomes bacteriologically positive again; and secondary relapse as relapse which occurs after a somewhat longer period of chemotherapy or after discontinuation of chemotherapy?

MR. EDWARDS: Yes, I think that that is a reasonable classification of the types of relapse in relation to chemotherapy.

DR. MIDDLEBROOK: In relation to chemotherapy?

MR. EDWARDS: If you are asking me from the surgical point of view, I should say that the relapse in surgery was any indication of active disease occurring at virtually any time after the immediate postoperative stage, shall we say, three months.

DR. MIDDLEBROOK: Do we have to define relapse in bacteriologic terms? Does it have to include bacteriologic considerations?

MR. EDWARDS: I think we ourselves as a group would take relapse as any indication, either bacteriologic, roentgenographic, or clinical, that things were not going accurately or well for the patient.

DR. MIDDLEBROOK: Dr. Raleigh, do you believe that relapse should be bacteriologically relevant or would you use the term without necessary relationship to bacteriologic considerations?

DR. RALEIGH: I think that you must use bacteriologic criteria for relapse. If we stop to think that the finding of tubercle bacilli in a patient's secretions is evidence of an actively sloughing tuberculous focus, I don't see how we can interpret bacteriologic findings any other way. I think that that is a very important aspect of relapse and indicates merely that the plateau achieved as a result of previous therapy is not being maintained. You obviously can't speak of relapse in a patient who has not achieved even this much of a plateau, that is, in one who has never "converted" his sputum, never closed his cavity, or never stabilizied his disease. You have got to achieve at least most of those criteria before you can start talking about relapse; but once you have achieved a plateau of improvement and stability, any deterioration of that situation, I think, should be called relapse.

DR. MIDDLEBROOK: You would, then, exclude the use of what we have already discussed as primary relapse in practice. You would not use what I defined as primary relapse as relapse? You would not call that relapse?

DR. RALEIGH: Relapse occurring during therapy?

DR. MIDDLEBROOK: Yes.

DR. RALEIGH: I am a little bit opposed to making the distinction on those grounds because I think a relapse occurring during the first year or the first eighteen months of therapy may mean one thing. However, to lump that with an occasional positive culture that occurs after three or four or five years of continuous isoniazid therapy such as was mentioned yesterday, I think would deprive the term of any homogeneity at all. I think you would have to define almost every case to understand what you really were talking about when you spoke of relapse during chemotherapy as one type of relapse and relapse after chemotherapy as another. I don't think that that particular distinction is going to be practically useful.

DR. MIDDLEBROOK: If a patient's sputum turns negative at two months and stays negative for four more months under treatment and the patient remains under treatment and becomes bacteriologically positive a month after that, say, in the seventh month, you do not consider that that is a relapse?

DR. RALEIGH: Oh, yes, I do. I think that is a relapse, but I don't think that that should be called a primary relapse and that a relapse in the fifteenth or eighteenth month in a patient who becomes negative at the second month and remains negative for a year and then has treatment stopped should be called a secondary relapse.

I think that the distinction between primary and secondary on the basis of whether chemotherapy is still being given is not a useful one. I think

perhaps primary relapse occurring during the first year of therapy might be one thing. Relapses occurring after that might be another, regardless of whether therapy was being continued or not.

DR. MIDDLEBROOK: Dr. Epstein, do you think it is not useful to distinguish between relapses that occur under chemotherapy and those that occur after discontinuation of a long period of chemotherapy?

DR. EPSTEIN: I really think we can lump them together. The big thing that enters here is: Has the patient been discharged by his physician as having received adequate chemotherapy and referred to the outpatient department? We have so many patients who feel so well after the first few months of therapy that they leave us, and they don't attend our clinic at all. There is no continuity of therapy. They may return in a worsened condition. We can lump those together.

I think that any patient who is getting adequate chemotherapy and continually gets adequate chemotherapy and then his disease worsens should be termed a case of relapse whether it occurs one year after chemotherapy or two or three years after chemotherapy. After all, why should a patient's disease worsen under adequate chemotherapy? Something has occurred so that his pathologic lesions become more extensive and sputum becomes positive for tubercle bacilli.

Our great problem these days, particularly in the city institutions, is that our patients leave us, and the setup, if you know New York City, is that the Board of Health may take care of them. Patient after patient has left without complete chemotherapy. When we follow them up, we find they don't attend the clinics. Are we going to lump those with the same persons who have had two years of chemotherapy? They are entirely different cases. One hasn't received enough chemotherapy; and, to our great horror, we do know that, in spite of adequate chemotherapy, the other still worsens.

DR. MIDDLEBROOK: Dr. Epstein, before we introduce psychologic, sociologic, or anthropologic problems, let us continue to discuss some of the more technical aspects of the problem of relapse. It seems to me that the members of the panel thus far have refused to consider—not necessarily with regard to this definition, but simply don't wish to consider—problems such as that of a patient who responds to chemotherapy, turns sputum negative in the second, third, fourth, or fifth month, and then becomes positive one or two or three months later.

Does the panel not wish to discuss this aspect of chemotherapy? In their experience if it doesn't happen, then, of course, there is no point in discussing it. Now, if it does happen, I would like to ask each member of the panel who has clinical experience just how often it happens in terms of percentages of unselected cases.

Mr. Edwards?

MR. EDWARDS: I don't think I can give you any accurate figures on the medical side of this.

DR. MIDDLEBROOK: It doesn't happen in England, according to Dr. John Crofton. Is that true?

MR. EDWARDS: I think it can happen. Perhaps it is not fair for me to comment on what Dr. Crofton says, but I think it can happen.

DR. MIDDLEBROOK: Dr. Bignall, doesn't it happen in England?

DR. BIGNALL: Dr. Crofton's experience is in Scotland.

DR. MIDDLEBROOK: I was talking about England. When I spoke to you I meant England.

DR. BIGNALL: Yes, of course, it happens.

DR. MIDDLEBROOK: Dr. Steele, does it happen in California?

DR. STEELE: Yes. I think slightly less than 10 per cent probably, if you are asking for statistics.

DR. MIDDLEBROOK: Yet in none of the statistics of the control studies of the Veterans Administration is it in fact (in the reported studies) less than 10 per cent; is that correct?

DR. STEELE: There has been only one Veterans Administration study on the matter of relapse and follow-up.

DR. MIDDLEBROOK: We have given up the word "relapse." We wouldn't agree to include in this problem of drug treatment failure during the first six months to a year, so we are just considering problems of patients who respond at first and then simply don't hold that response, become bacteriologically negative and then become positive again within a matter of a few months.

DR. STEELE: I think you better ask someone else about the Veterans Administration.

DR. MIDDLEBROOK: Dr. Tucker?

DR. TUCKER: This will have to be based upon a very unreliable memory, Dr. Middlebrook, but I do believe that there have been tables in the published transactions of a number of our recent conferences which give figures on the rate (at

different times after the initiation of original treatment) at which patients who have become negative and stayed negative for a period, again became positive. I don't remember whether it is two or three months (maybe Dr. Raleigh does), but it is certainly a minimum of two and probably three.

If this is what you are asking about, yes, of course, there is such an incidence. In the period between four and eight months after the start of original treatment this is very low. I am tempted to say 1, 2, or 3 per cent, but these figures may not be reliable. Then there is a progressive increment, but it is not of a high order and I don't believe that it approaches the figure of 10 per cent. I doubt if Dr. Steele was referring to that.

DR. MIDDLEBROOK: So that in the Veterans Administration experience most of the patients who do not respond to original chemotherapy with standard regimens never do turn bacteriologically negative, and therefore never could be considered to have any kind of relapse in any sense; is that it?

DR. TUCKER: In the Veterans Administration figures we make a clear distinction between failures to convert and those who have converted for a stated period of time and then again become positive bacteriologically.

DR. MIDDLEBROOK: Dr. Steenken, I remember you once gave an extensive discussion of this problem of early bacteriologic response. Would you like to discuss this? Is there such a thing as bacteriologic response to negativity or close to negativity and then a bacteriologic relapse regardless of the general clinical situation?

DR. STEENKEN: If you hadn't brought that question up I was going to bring it up myself. I think bacteriologic relapse needs much more clarification in that, even before the days of chemotherapy, as many of you will remember, patients were treated, and their sputums were negative and stayed negative for long periods of time; they were discharged and went home. Dr. Medlar published a series in which he had done gastric lavages on these patients and noted many positive findings without clinical relapse.

If one colony is found and the patient never shows a deterioration by X-ray or any clinical study, I think that patient handles his tuberculosis just as well without chemotherapy. Unless you get a "high positive" I think that the presence of a few tubercle bacilli does not necessarily mean a relapse.

DR. MIDDLEBROOK: Before we discuss the problem of relapse, after what the panel seems to agree upon thus far, that is, a long period of negativity, I think it is important to discuss those problems that are met with from the very beginning. With our present modes of antimicrobial therapy, the results are simply not perfect even at that early stage. Thus, one should anticipate that, although patients may become bacteriologically negative (and this may not necessarily be attributable to any antimicrobial therapy), they may not remain so; and these problems have to be considered before late relapse can be discussed.

Dr. Paul Chapman has a large outpatient clinic and he must have some experience as to what proportion of patients who are ambulatory fail to convert during the initial period of treatment with drugs on an outpatient basis, and what proportion become "negative" for a period of a few months and then become bacteriologically positive again during the first six or eight months of chemotherapy.

Would you say something about this, Dr. Chapman?

DR. CHAPMAN: Our clinic is set up on the basis of discharged patients who have apparently converted to negativity, so our relapse rate is on the basis of what we consider a true bacteriologic relapse. Some of the patients do "relapse" quite early and this, of course, means that we must have misinterpreted what we were doing. But we do not usually initiate therapy in the clinic. All kinds of relapses run about 7 per cent in our experience, that is, clinical and bacterial, but these are supposedly true relapses, not failures to convert.

DR. MIDDLEBROOK: Before we go on, perhaps we ought to ask other members of the panel whether they agree with Dr. Raleigh that any relapse must have bacteriologic confirmation. Would you agree to that, Mr. Edwards?

MR. EDWARDS: No, not at all. I think that many relapses can be bacteriologically negative, but roentgenographically there can be very considerable evidence of deterioration without any development of the positive sputum, at any rate in the methods that we use to find it.

DR. MIDDLEBROOK: Dr. Steenken, do you agree that relapse must be bacteriologically demonstrated?

DR. STEENKEN: Oh, no. I think some of our most important ones, our worst ones, may still have negative secretions.

DR. MIDDLEBROOK: Dr. Froman?

DR. FROMAN: Would it be possible that, although there is a relapse and it is considered to be negative, that is, we just can't demonstrate the positivity of the relapse, there is still a bacteriologic problem involved?

DR. MIDDLEBROOK: Dr. Auerbach?

DR. AUERBACH: It is a little difficult for me to believe that tubercle bacilli are getting out of the cavity, spreading to other parts of the lung parenchyma by way of the bronchi, therefore indicating that the tubercle bacilli are in the bronchi and yet can't be found in the sputum.

DR. MIDDLEBROOK: Dr. Epstein, what is your opinion? Does relapse necessarily require that there be bacteriologic evidence to call it relapse?

DR. EPSTEIN: I wouldn't like very much to get into an argument with the bacteriologists and pathologists we have on the panel; but, of course, if I see a case of disease that is spreading and our methods of examination do not show tubercle bacilli, I begin to think that perhaps our methods are wrong, are not adequate. We do know that the bacilli may not grow on the culture. You may see them. We have seen cultures grow after three or four months of incubation. Our friends have shown us resected specimens that were negative and which grew tubercle bacilli as long as six months later. So perhaps our methods of examining the sputum are wrong. Certainly, if we see a lesion in the lung that is spreading and we cannot say it is due to nonspecific causes, then it must be due to tuberculosis.

DR. MIDDLEBROOK: Dr. Epstein, you depend then more upon the roentgenographic than upon the bacteriologic members of your team.

I would like to have yes or no answers among the orbital panel. Does relapse, as you would like to have us discuss it, gentlemen, necessarily have to have accompanying bacteriologic evidence that tubercle bacilli are involved in whatever one is observing clinically?

Dr. Canetti?

DR. CANETTI: If you want a clear-cut answer, certainly "no" as to the bacilli in the sputum. Of course, bacilli are involved in the lesions.

DR. MIDDLEBROOK: That is on a theoretic basis, so you won't help the clinician in defining what he will call a relapse. Dr. Raleigh insisted that there must be bacteriologic proof.

DR. CANETTI: I disagree with that. I agree with Mr. Edwards that there can be a good deal of roentgenographic relapse without bacteriologic proof.

DR. MIDDLEBROOK: Dr. McDermott?

DR. MCDERMOTT: I am with the Edwards-Epstein position.

DR. MIDDLEBROOK: You also believe more in looking at X-rays than listening to bacteriologic results?

DR. MCDERMOTT: I think Dr. Epstein has his finger on the thing. Certainly the tubercle bacilli are in the sputum, if it is a relapse, as Dr. Auerbach said.

DR. MIDDLEBROOK: Then you agree with Dr. Raleigh.

DR. MCDERMOTT: No, I don't. Equally obviously, as Dr. Epstein says, you can't always culture bacilli to demonstrate them.

DR. MIDDLEBROOK: Dr. Raleigh?

DR. RALEIGH: I think when we are trying to establish a fact, namely, the fact or the incidence or the prevalence of relapse, that we have to be perhaps stricter in our definition of relapse than we might be as far as the clinical management of the patient is concerned. I think, however, that the incidence of intercurrent nontuberculous pulmonary disease, often chronic and protracted in its course, particularly in patients in the age group with which we have to deal, should not be confused with a possible tuberculous relapse. Patients in this group are inpatients who have unquestionably had tuberculosis.

My point is: For the purpose of determining the incidence of relapse and, subsequently, what should be done about it, I think we should not count as relapse anything which is not bacteriologically proved. I don't deny for a minute that there may be occasional unfavorable X-ray changes which are truly tuberculous in nature, in which careful and repeated search for tubercle bacilli fails to reveal tubercle bacilli. But I don't think that these can be distinguished frequently from nontuberculous pulmonary disease, and I think for the purposes of this discussion that they should be excluded.

DR. MIDDLEBROOK: For study purposes you think it is essential that there be bacteriologic proof. This is a little different from practice. Would you require this for all private patients, if you had any private patients?

DR. RALEIGH: I would require this proof before I would call such a case a relapse in any study

that I was conducting or reporting. Whether I would require this for the management of the patient—in other words, whether I would base re-treatment with antimicrobial agents or possibly even resection on the presence or absence of tubercle bacilli in the sputum is an entirely different question. I probably would not, but I think for the purposes of reporting the incidence of relapse only those relapses which are unequivocally and demonstrably tuberculous should be counted.

DR. MIDDLEBROOK: I see two surgeons sitting in the audience. It seems to me this is a problem which surgeons are often faced with. Dr. Wilson, what is your opinion on these problems: no evidence, no bacteriologic proof, but everyone tends to agree this is a relapse.

DR. WILSON: We use everything, roentgenographic relapse and bacteriologic relapse. We have trouble proving bacteriologic relapse in the face of some of the worsening X-rays. I agree with what Dr. Epstein says.

DR. MIDDLEBROOK: Dr. Chamberlain?

DR. CHAMBERLAIN: I agree.

DR. MIDDLEBROOK: Dr. Sommer?

DR. SOMMER: I understand just what Dr. Raleigh is talking about, but from the clinical standpoint I think I must go along with Dr. Epstein and Dr. McDermott.

DR. MIDDLEBROOK: The dissociation between study purposes and practical clinical work: Is this based upon a lack of confidence in bacteriology laboratories, do you think, Dr. Steenken?

DR. STEENKEN: That is what I was just whispering to Dr. Steele. They try to "sell the laboratory short." The laboratory techniques are not as bad as the clinicians would like you to think they are because they can't show tubercle bacilli when there is relapse. I always like to relate to the days before chemotherapy. Since chemotherapy, things are more complicated. As you know, with the change in virulence of the tubercle bacillus with the use of isoniazid, you can't get a positive guinea pig test from a culture with this much more sensitive method. But in the techniques before the days of chemotherapy many of you men will recall patients who had large amounts of cavitary disease; and on repeated smear and gastric lavage morning after morning and night after night, it was not possible to demonstrate tubercle bacilli. Still the patients' disease was spreading. You remember many of those cases, and we had good laboratory techniques.

DR. MIDDLEBROOK: We often forget about the pediatrician. The pediatrician often has difficulty identifying tubercle bacilli in the excretions or pathologic materials from his patients, and he is faced with this often in trying to decide whether or not a child has had a relapse, either during antimicrobial therapy or after discontinuation of antimicrobial therapy.

Do you depend upon bacteriologic results, Dr. Lincoln, or do you go upon other variables, as Dr. McDermott and others have preferred to do?

DR. LINCOLN: We depend on bacteriologic results to a large extent, but we would not exclude relapse because of a negative bacteriologic result.

DR. MCDERMOTT: May I say I completely agree with Dr. Raleigh, and please don't cite me as saying that, in the inclusion of measurements for research purposes, nonbacteriologic cases should be included.

DR. MIDDLEBROOK: Shall we discuss this whole problem in relation to study purposes or in relation to practice?

MR. EDWARDS: I prefer we discuss it on the basis of study.

DR. MIDDLEBROOK: Dr. Raleigh, do you want study or practice?

DR. RALEIGH: Why don't we just separate the two and discuss them both? I think there is room for discussion of both, and I think that, if we make these distinctions as we go along, we can still keep our thinking straight. I think we can follow two trains of thought at once.

DR. MIDDLEBROOK: Dr. Robson, we haven't asked you yet what your opinion is on this.

DR. ROBSON: Obviously I can't speak from the clinical point of view, but I personally would regard relapse as what occurs when therapy has been successful and at the cessation of therapy something happens and the patient gets worse. From a bacteriologic point of view I can think of a lot of instances experimentally in which we have been totally unable to show tubercle bacilli by any cultural method, and we have tried very hard indeed; and yet on inoculation into guinea pigs we have gotten positive results. Although I think the bacteriologists have been doing a good job, the fact that no bacilli are found on culture is to me no definite evidence that bacilli are not present. I am quite positive of that from the experimental point of view.

DR. MIDDLEBROOK: Let us move to another problem. Obviously, it is not really important to decide this question here. As we wish we can refer to relapse for study purposes in that frame of

reference, or to relapse in practice if we feel like discussing it in that fashion.

There are very well established statistical data on the relapse rate of patients who have responded to therapy of pulmonary tuberculosis in the pre-antimicrobial era. The curves of the rate of relapse are quite well defined and agreed upon by several groups. They are, however, perhaps being used in relation to chemotherapy when there is no particular necessity that this should be the case. Is it possible that the relapse rate curve after discontinuation of chemotherapy will follow the same pattern after antimicrobial therapy as it followed in the pre-antimicrobial era?

Dr. Steele?

Dr. Steele: I have no definite figures on the subject. Personally, I don't think we have had time enough to answer that question. We haven't been using long-term chemotherapy for a long enough period of time to really know what we are talking about as far as that is concerned.

Dr. Middlebrook: Dr. Auerbach, let us discuss briefly the relevance of this problem to the nature of the lesions which exist in patients after apparently effective antimicrobial therapy, on the one hand, and after pre-antimicrobial therapy on the other.

Dr. Auerbach: Are you talking now of the basic pathologic lesions? May we confine it to the tuberculous cavity?

Dr. Middlebrook: No.

Dr. Auerbach: We have one hour and ten minutes. You wouldn't want me to discuss the comparative pathologic anatomy between the tuberculous lesions before chemotherapy and after chemotherapy, would you?

Dr. Middlebrook: If it is your opinion that primarily organisms in the cavity are the agents of relapse—whether or not bacteriologists can demonstrate the organisms which are the agents of relapse and you, therefore, wish not to bother about the nodular lesions in which excavation has never taken place—then I think this is permissible. Is this what you wish to do?

Dr. Auerbach: Let us say this, that basically the lesion in tuberculosis that you are treating is the cavity and, if you are going to get a relapse, the relapse I presume will be from the tuberculous cavity. Isn't that your assumption?

Dr. Middlebrook: Is that your assumption?

Dr. Auerbach: It is mine, definitely.

Dr. Middlebrook: All right, then we'll discuss the cavity.

Dr. Auerbach: I think that the tuberculous cavity in the era prior to chemotherapy closed and the bronchial communication remained closed. Following chemotherapy the cavity closes with inspissation of the necrotic material and the bronchus remains open. The question arises in the post-chemotherapy cavity: How long and how quickly can calcification occur in that necrotic material and, with that calcification, the death of the tubercle bacilli? That is the main difference between the two.

Dr. Middlebrook: Does calcification have to occur for death of tubercle bacilli, Dr. Canetti?

Dr. Canetti: Certainly not.

Dr. Middlebrook: Did you imply that you thought calcification had to occur in order to have tubercle bacilli sterilized by the host?

Dr. Auerbach: Quoting Dr. Canetti's own studies, I think he showed that, whether the patients received chemotherapy or not, the more calcified the lesions, the more difficulty he had in demonstrating tubercle bacilli in those lesions. I think I am correct in that assumption. And I think also it has been shown in the primary focus that the more calcium in the foci, the less the opportunity to grow tubercle bacilli. So, as a pathologist examining these lesions I would say that on that basis I made the statement. Dr. Canetti's work has been verified in subsequent studies by Dr. Hobby and also by Drs. Hall and Gleason.

Dr. Middlebrook: Dr. Canetti?

Dr. Canetti: This is a very complicated situation. First of all, it is absolutely true that bacilli are found very seldom in calcified foci: This is a very old thing.

Dr. Middlebrook: Stainable or unstainable?

Dr. Canetti: Unstainable as well; one finds just nothing. Here, we are speaking about cavities. It happens very often that calcifications are found in treated or untreated cavities. I have material of a little over six hundred cavities, and calcifications have been found in this material in 18 per cent of cases, which is a lot. These are precalcifications which are just lying in the cavity, small ones or bigger ones. In my opinion, these calcifications existed prior to treatment. They are old calcified foci which have just been liberated into the cavity by the softening process, so these calcifications which are very frequently found in cavities are no sign of healing whatsoever. They just existed prior to the treatment. These are the stones which are sometimes eliminated by some patients.

Now, the problem, in my opinion, is this: What happens to the cavity under treatment? There are two great issues, as you know: inspissation or open healing. The whole problem is: What are the rates of negativity achieved by one or the other way of healing; and, if some bacilli remain in inspissated cavities, on the one hand, or in open-healed cavities, on the other, what are the numbers of bacilli found? That is the whole problem.

The third problem is: Is the bronchus open or not? These are the main factors.

DR. MIDDLEBROOK: Without regard to the properties of the organisms that are left, are they drug susceptible or drug resistant? You mentioned numbers, but what about this other factor?

DR. CANETTI: It does have great importance, but it is another problem. I am just speaking about the main infective factors, the presence of bacilli, numbers of bacilli, and open bronchial communication, on which Dr. Auerbach has already laid great emphasis.

DR. MIDDLEBROOK: Dr. Auerbach, when relapse does occur after discontinuation of chemotherapy, which is the commoner: relapse with drug-susceptible populations of tubercle bacilli, when bacteriologists can isolate them, or with drug-resistant populations?

DR. AUERBACH: Relapse is far more frequent with drug-resistant populations.

DR. MIDDLEBROOK: Dr. Steenken?

DR. STEENKEN: I think Dr. Raleigh has a better answer to that.

DR. RALEIGH: I wish you would restate the question.

DR. MIDDLEBROOK: When relapse does occur after twelve to eighteen months of multiple-drug original chemotherapy, which is the commoner: relapse with the excretion of populations of tubercle bacilli that are drug susceptible (susceptible to the drugs that have been employed) or resistant to the drugs that have been employed?

DR. RALEIGH: I think drug-resistant bacilli. There are occasions of relapse with drug-susceptible organisms, particularly when it is a relapse of a closed noncavitary lesion, but in cases in which the disease has been cavitary and has achieved inactivity or target point and then has relapsed, the tubercle bacilli are most likely to be resistant to at least one and possibly to more than one of the drugs that have been given.

DR. MIDDLEBROOK: Dr. Steele?

DR. STEELE: My impression was just the opposite. I admit that I haven't had too many cases, but I am basing my impressions on the bacteriology of resected specimens following a relapse. It is my impression that these bacilli are susceptible.

DR. MIDDLEBROOK: Dr. Canetti, you have done a good many bacteriologic studies on resected specimens. What is your experience?

DR. CANETTI: My experience is that, if relapse occurs after treatment of cavitary tuberculosis and if the relapse involves reopening of the cavity, or something like that, in the great majority of cases the bacilli are resistant.

DR. MIDDLEBROOK: Dr. Epstein?

DR. EPSTEIN: With regard to this problem, I would agree that once the cavity opens and there is evidence of worsening the bacilli are not only there, but that they are resistant.

DR. MIDDLEBROOK: Does anyone other than Dr. Steele and myself have the experience that the bacilli are usually drug susceptible? Dr. D'Esopo?

DR. D'ESOPO: I wouldn't say that they are usually drug susceptible, but we have found a number (I can't say how many) that are drug susceptible after relapse. I think that the generality that they are usually resistant is incorrect.

DR. MIDDLEBROOK: Dr. McDermott?

DR. MCDERMOTT: I think it depends to some extent on whether you are talking about relapse during therapy or relapse after therapy.

DR. MIDDLEBROOK: After discontinuation of therapy.

DR. MCDERMOTT: Then I think they are more apt to be susceptible.

DR. MIDDLEBROOK: You can see that there is disagreement on this point. Any more discussion on it?

DR. D'ARCY HART: I would like to answer by asking a question. It must be that if you give too short a course of therapy—

DR. MIDDLEBROOK: Twelve to eighteen months.

DR. D'ARCY HART: You are sticking to that?

DR. MIDDLEBROOK: Yes.

DR. D'ARCY HART: I see. I'm sorry.

DR. CANETTI: I think we should go a little deeper into what sort of resistance we are speaking about. I am speaking about isoniazid resistance, and I must again repeat that in my studies the great majority of cases in which the cavity shows the bacillary population remaining after

such treatment, these bacilli are isoniazid resistant although they may be resistant to a very low level. This is a very important question. They might not be considered as resistant with certain standards, diagnostic standards of resistance; but, nevertheless, they are resistant if standards are changed. The occurrence of purely isoniazid-susceptible bacilli in cavities after long treatment is limited to very rare cases; and in these cases the bacilli are ordinarily very few, just a few persistent ones, as has been described by Dr. McDermott. For other drugs this doesn't hold true, of course.

DR. MIDDLEBROOK: Not for streptomycin?

DR. CANETTI: Not for streptomycin and not for PAS.

DR. MIDDLEBROOK: Even when streptomycin is given in dosage of the order of a gram daily?

DR. CANETTI: Certainly.

DR. MIDDLEBROOK: There seems to be disagreement on this point. The reason why I am emphasizing it is that it leads us directly into the problem of the host responses. If these organisms stay in the host, whether they are drug susceptible or not, but more particularly if they happen to be drug susceptible, indicating that the drugs had not affected the population from which the agents of relapse derive, then it means that there is a deficiency on the part of the host.

I believe that Dr. Robson has some experimental studies in mice which are quite relevant to this problem. Dr. Robson, would you present your material, please?

DR. ROBSON*: In the first place, I should like to emphasize that I speak essentially as an experimentalist and not from the clinical point of view. Moreover, I am essentially a pharmacologist and have little knowledge of bacteriology. I hope, however, that I shall not ignore the clinical implications of the work discussed. The problem of relapse after antimicrobial therapy has, of course, been extensively discussed before and I should like to draw attention particularly to two of these discussions, namely, that by a panel of the American Trudeau Society (Am. Rev. Tubere: 1953, *67*, 680) and second, the detailed and wise discussion by Canetti in chapter 5 of his book *The Tubercle Bacillus in the Pulmonary Lesions of Man*. Canetti has in particular emphasized the importance of establishing what is actually due to chemotherapy and what is due to natural defenses and to immunity. He says (on page 159): "A thorough knowledge of the anatomic and bacteriologic aspects of human tuberculosis, untreated by chemotherapy, is required so as not to attribute to chemotherapy what is usually found without it." I think this consideration must consistently be in mind in trying to assess the value of chemotherapy.

I shall try to consider the problem under four headings:

1. The viability of bacilli which remain after prolonged chemotherapy. It is well known that after many months, or even after a year of chemotherapy, many bacilli can be demonstrated in lesions by staining methods, and many such bacilli apparently stain quite normally. It must, however, also be recognized, as Canetti has emphasized, that such stainable bacilli were also found in healed lesions before the era of effective chemotherapy. The problem is whether any such bacilli usually remain alive, or whether they are all dead in most cases.
2. The breakdown of lesions after prolonged chemotherapy. It is well known that this can occur. For example, in the clinical investigations done at Guy's Hospital, it has been found that not infrequently patients with chronic pulmonary tuberculosis treated over quite long periods will relapse after cessation of treatment (Joiner *et al.*: Lancet, 1956, *2*, 165). There are, of course, also instances of relapse long after cessation of chemotherapy. On the other hand, it is quite possible that relapse may not occur, even though viable bacilli remain present in the treated lesion.
3. The spread of organisms (*M. tuberculosis*) from the infected focus to other parts of the body during and after cessation of prolonged chemotherapy. This may not occur even though viable bacilli remain present in the primary lesion.
4. The development and maintenance of immunity during and after cessation of prolonged chemotherapy. Immunity is of importance not only as a mechanism which may prevent the breakdown of a treated lesion, but also as a defense against subsequent reinfection.

The problems I have just discussed have so frequently and extensively been considered that it would be easy to go over the same ground and merely repeat what other people have said. Since we have recently investigated these problems by rather new techniques, I thought it advisable first of all to discuss the problem in general and

* The following represents a statement prepared by Dr. Robson for insertion in place of his remarks.

the issues involved and then to go on to a description of some of our own investigations to see what light they may throw on the problems raised. I have taken this course particularly since, within the limits of our experimental methods, there are definite answers to some of the problems raised. Whether these answers are also valid for human tuberculosis is a question that remains to be discussed. Our own work has essentially been performed on experimental tuberculosis of the cornea in mice, and I am going to describe some of these results. I would like to add, however, that we are trying to develop similar techniques for the investigation of primary tuberculosis of the lung in mice. We have used experimental corneal tuberculosis since it is a technique which allows us to measure reasonably accurately: the course of the disease as assessed by various macroscopic and microscopic techniques; the multiplication of organisms and the total number of organisms (viable and nonviable); the spread of the disease and of mycobacteria to other parts of the body; and the extent of the immunity present in the animal.

Following intracorneal inoculation with *M. tuberculosis* in mice, there is a gradual development of a lesion, at first visible only microscopically, i. e., by phase contrast examination of the whole cornea (Robson and Dideock: Am. Rev. Tubere., 1956, *74*, 1) or by staining the whole cornea (Robson and Sullivan: Am. Rev. Tubere., 1957, *75*, 756) and later visible macroscopically. After some weeks the macroscopic lesion reaches a maximum when it involves much of the cornea. During this period there is a constant multiplication of mycobacteria to reach a maximum after some weeks, after which the total count of stainable organisms remains steady.

On investigating both the viable and stainable counts, it is found that they are the same for about a fortnight, after which a precipitous fall in viable count occurs which reaches very low values after some weeks. During the development of the corneal lesion, immunity gradually develops so that a week after inoculation the challenge of the other cornea with a small inoculum no longer produces a macroscopic lesion, though some multiplication of organisms still occurs. This immunity reaches a maximum after about one month, at which time a small challenge inoculum put into the other cornea no longer shows any multiplication, and immunity remains present for many months after inoculation. It seems quite likely that the development of this immunity explains the precipitous fall in the viable count in the cornea which occurs about a fortnight after inoculation. This problem is being further investigated.

Careful examination of the organs at various periods after corneal inoculation in mice shows no evidence of any systemic spread for one to two months. In particular, the lungs are quite free of disease and of mycobacteria. After many months, however, extensive pulmonary disease develops, and many stainable and also viable organisms can then be found. An important question which is not one of the main issues discussed at present is the reason why disease develops in the lungs when sufficient immunity is present to prevent any multiplication of a challenge infection in the cornea and when, moreover, such immunity is presumably killing off organisms rapidly in the cornea.

When isoniazid is given to mice for a period of twenty-eight days, starting at the time of intracorneal inoculation, the infection is held in abeyance. When the dose is about equivalent to the therapeutic dose in man, i.e., 0.3 mg. per mouse per day, then cessation of treatment is followed by multiplication of organisms and by the ultimate appearance of a macroscopic lesion which develops in the same way as a primary inoculum. These doses of isoniazid, therefore, merely hold the infection in check. Ten times such a dose, i.e., 3.0 mg. per mouse per day, can, however, safely be given to mice and, when such treatment is applied for a period of twenty-eight days, starting at the time of inoculation, cessation of the treatment is not usually followed by much bacterial multiplication, and macroscopic lesions develop only occasionally and sometimes many weeks after the end of the treatment. This is so even though viable organisms are present in the cornea.

We were, therefore, interested to find out what would happen if chemotherapy was applied over really long periods, i.e., periods equivalent to those used for the treatment of pulmonary tuberculosis in man. In this investigation a large number of mice were inoculated and left untreated for a fortnight, during which all had developed a macroscopic tuberculous lesion at the site of inoculation of the cornea. These mice were then divided into two groups, one of which was left

untreated to act as control and the other treated with large doses of isoniazid (3.0 mg. per mouse per day) for a period of eleven months. After this time the treatment was discontinued and the animals were observed for a further period of eight months to see whether any changes occurred in the corneal lesion. The whole experiment, therefore, was spread over a period of nineteen months, the aim being to have a period of treatment similar to that used in human disease and to use intensive therapy in order to obtain an optimal effect in the hope of producing full eradication of the infection.

* * *

The initiation of the isoniazid treatment prevented any further increase in the size of the macroscopic lesion in the cornea which did occur in the control. There was some decrease in the size of the lesion which was essentially due to clearance of perifocal inflammation (as shown by microscopic examination of the cornea). This was the average result, but it must be emphasized that occasionally in the treated animals the macroscopic lesion disappeared completely, leaving only a microscopically visible lesion.

On cessation of the eleven months' treatment with isoniazid, there was no breakdown whatever of the lesions during the observation period of eight months. The treatment, moreover, prevented any increase in the total number of organisms present in the cornea, as did indeed occur in the control group of animals (the total number of organisms in the cornea was assessed by staining the whole cornea and using the method of Robson and Sullivan). On the other hand, the prolonged treatment produced very little decrease in the number of bacteria present in the cornea during the period of treatment and during the subsequent observation period of eight months, i.e., the bacteria throughout this nineteen-month period remained *in situ* and, moreover, remained within cells. Some degeneration of the organisms, however, did occur during this lengthy period, so that by the end of it about half were present as beaded forms and there were also some globules of acid-fast material, presumably products of the further degeneration of mycobacteria. The remainder still continued to be morphologically normal when stained with carbolfuchsin. In the control animals, however, (which of course, had received no chemotherapeutic treatment) a similar percentage of the organisms had undergone the same type of degeneration so that the prolonged chemotherapy does not seem to have accelerated the degenerative changes in the mycobacteria.

Twelve corneas from the treated group were cultured in various media (eight months or more after the beginning of treatment) and in no case was there any growth of mycobacteria. During this same period, 7 corneas were put into guinea pigs. Three of these failed to produce any disease; in two cases it is too early to judge the results, but two corneas removed fifteen months after inoculation, i.e., four months after cessation of the eleven-month chemotherapeutic treatment, produced tuberculosis in the guinea pigs. It is thus clear that viable organisms can remain in the cornea after a long period of intensive isoniazid treatment. In control animals, incidentally, 12 of 12 corneas were negative by cultural methods and 5 of 5 were negative on guinea pig inoculation.

The effect of the treatment on the spread of infection was very striking. This was practically completely prevented so that no gross disease was found in the lungs or in any other organs. Occasionally minute lesions were present in the lungs, but no acid-fast bacilli could be recovered from them with one exception, in which a few acid-fast bacilli were found in the lung smear of a mouse which had died from an intercurrent infection; this may well have been purely a coincidence. It will be remembered that extensive pulmonary and other systemic disease had developed in the control animals during the same period.

In untreated animals it has been shown that immunity is present for long periods, certainly for more than a year (Acharya, *et al.*: Am. Rev. Tuberc., 1958, *78*, 203). The antigenic stimulus for such immunity is present at first in the cornea and subsequently, of course, in the lungs and in other organs in which tuberculosis develops. With the intensive treatment used in the present investigation, there was only slight immunity five months after the commencement of treatment, and after thirteen months no immunity could be detected. This shows, therefore, that the treatment led to the disappearance of the immunity.

In summary, therefore, our experiments have shown that intensive chemotherapy of established corneal tuberculosis in mice prevents any further growth of the lesion and any further multiplica-

tion of bacilli. After cessation of such treatment no breakdown of the lesion occurs. The treatment also prevents the systemic spread of the disease, but, on the other hand, abolishes the immunity. It does *not* consistently kill all of the organisms.

Certain problems need special consideration. First, to what extent does intensive and prolonged chemotherapy kill organisms, compared with the effects produced by the natural defenses of the body and immunity. It is interesting that live organisms were indeed recovered from corneas of animals subjected to prolonged chemotherapy whereas none were recovered in the control group. The numbers are not sufficiently large to make the difference significant, but the results are nevertheless suggestive. They raise one particular question: in the chemotherapy of human tuberculosis, would it be worth while to have periods of treatment alternating with periods of no treatment in the hope of completely checking the disease and yet preserving the immunity to tuberculosis? A further point which, in fact, Canetti has already emphasized, is that our present drugs, though highly effective in controlling tuberculosis, are by no means effective in killing the organisms in a resting stage. Obviously, further work is necessary in the hope of finding new drugs which will be able to accomplish this.

Dr. Middlebrook: Thank you, Dr. Robson. This sounds like a beautiful experimental model. The results remind me somewhat of the results that Dr. McCune obtained in Dr. McDermott's department. I wonder if Dr. McDermott has a comment to make about the difficulty of identifying any viable cells immediately after the discontinuation of single- or double-drug treatment of mice and their ability to show their presence some months later by virtue of either clinical relapses of mice or by bacteriologic methods.

Dr. McDermott: I think that in infectious diseases in general today we are becoming much more aware of the problem of latent infections, namely, infections which cannot be demonstrated by any of our available methods, yet which, nevertheless, are there. To take a laboratory example, much of our tissue culture work today is being affected by the fact that apparently sterile mammalian cells put into tissue cultures nevertheless do contain infective agents which emerge gradually. That is why we have to be so very careful about putting much weight on the failure to demonstrate tubercle bacilli in tissues since we have this enormous background of experience from microbiology in general.

I think that what Dr. Robson has found is in essence quite in agreement with our notions on microbial persistence and that it is microbial persistence that is the important reason for our therapeutic failures.

I have just one more point. I think we have been tending to regard host defenses as a sort of a "cop on the beat" and, if the cop's eyes are turned momentarily, "the boys will get to the candy store." This is not necessarily true. The possibility that tubercle bacilli can, like other microorganisms, go into stages in which they will persist in these stages quite independently of anything else for very long periods of time is present. Thus, we need not necessarily expect that the mere presence of bacilli should necessarily be reflected in relapse. It may not be reflected in relapse for five or ten years thereafter; but, nevertheless, the microorganisms are there and have the potential to cause relapse.

Dr. Middlebrook: Dr. Youmans, you have had a good deal of experience in this sort of business, and I wonder if you have made any observations which you think are relevant to this problem, that is, chemotherapy and host factors in relation to persistence or latency.

Dr. Youmans: I can make a comment in regard to the phenomenon of the drug susceptibility after prolonged periods in the tissues, not from work of our own; but essentially this is a repetition I think of what I said yesterday, and it follows also from Dr. Robson's findings. The occurrence of drug-susceptible organisms in relapses after long periods of therapy is not to be wondered at at all, because drug resistance can only occur, or, let us say, the emergence of drug-resistant populations can only occur under conditions in which there is bacterial multiplication. Under conditions in which there is bacterial persistence, whether it is in a closed lesion of a human being or in the experimental animal such as Dr. Robson has described, or in work like Dr. McDermott has done in his own laboratory, the microorganisms in these situations are not multiplying by virtue of the activity of the acquired resistance. Even though drug-resistant mutants may occur, these cannot emerge into significant populations unless they are able to

multiply. Under cover of therapy, such resistant or susceptible microorganisms will not multiply under the conditions specified because the forces of acquired immunity hold them in abeyance.

Under these conditions, then, two bacteriostatic mechanisms are operating: on the one hand, the drug; and, on the other hand, the bacteriostatic mechanisms of acquired resistance of the host.

DR. MIDDLEBROOK: Dr. Canetti has emphasized the importance of the numbers of organisms involved. I am sure that for you there is a difference between a little lesion in the eye of an experimental animal and a cavity in a human being. Would you comment on this in relation to drug resistance and microbial persistence, and so forth?

DR. CANETTI: This is a very important point. The numbers of bacilli which exist in the cavity before treatment may be very different from one case to the other. On the average, however, if it is a real cavity with an open bronchus and positive sputum, the number is extremely high. I have tried some evaluation of this number and I have come to the conclusion that the total number of viable bacilli which may exist in a cavity of two centimeters in diameter before treatment may amount to one billion, 10^9. In such a population the number of isoniazid-resistant mutants which may exist may be as high as 10^3, or even 10^4. This shows that in this cavity a non-negligible resistant population, so to speak, may exist before any treatment.

If treatment is such, or if the conditions are such, that there is a failure—say that the second drug doesn't work for some reason—then it is evident that the existing mutants will be selected out. This doesn't mean that in every case these mutants will multiply to a great extent; and here I might state two different things which occur in these cases which are, on the whole, failures.

In one type of case the mutants do multiply and we find very high numbers of resistant bacilli in these cavities. This is a frequent occurrence, but by no means the only possible one. In other cases, although the selection of these mutants has occurred, the number of resistant mutants which is found in the cavity after, say, one year of treatment or even more, is extremely low and there may be as few as only one, two, or three isoniazid-resistant colonies which are isolated out of the entire cavity.

The resistant mutants which are isolated in this case behave exactly like persisters. They are persisters in the sense of what Dr. McDermott and Dr. Robson said. They exist in tissue under conditions in which they just don't multiply. They are alive. They are there; they don't multiply, but they are persistent.

I mean that we should not appose susceptible persisters so strongly, on the one hand, and resistant bacilli, on the other hand, because we might have susceptible persisters (as in these experimental conditions) which are very different from those that exist in a cavity.

Great numbers of resistant bacilli might have multiplied under certain conditions and then there might be resistant persisters, that is, very few resistant bacilli, which have been selected out and which have not multiplied and have remained in these cavities.

DR. MIDDLEBROOK: I am glad you pointed that out, Dr. Canetti, because I think it has been commonly viewed that persisters are drug-susceptible organisms simply because under the experimental model of the laboratory one is usually not dealing with population cycles, but that both drug-susceptible and drug-resistant microorganisms can be persisters. This is in summary what you are saying.

Dr. Steenken has had experience with the emergence of drug-resistant populations and with persisters in experimental animals.

DR. STEENKEN: It is interesting to hear Dr. Robson who is carrying on work almost identical with ours at the Trudeau laboratories. In fact, I have a few slides in my pockets and, if anyone would like to see them, I will be glad to show them. We have tried to set up experiments and answer several questions concerning drug therapy; we have used experimental rabbits and produced inhalation tuberculosis, that is, solitary caseous lesions as well as cavitary disease. We were trying to answer two questions:

Whether after long-term therapy, if a lung on one side was removed and overdistention was produced, a lesion in the other lung would be reactivated; and whether that lesion would be reactivated more readily if resistant organisms were present.

To be brief, let me say that some of the rabbits were treated for as long as eighteen months, then were taken off the drugs to see whether they would relapse after that period of time, and were

followed by X-ray. Many of the lesions went on to calcify; some did not calcify. We removed the lung on the opposite side of wherever the remaining lesion was in order to produce overdistention. Pathologically we produced beautiful overdistention, and some of the rabbits have had this overdistended lung for a year and a half without reactivation of the disease.

When we removed the lesions and did the bacteriology as well as animal inoculation and cultures by every technique we possibly could use, it was very interesting to find that we had duplicated what you are finding in human beings. This was very important because we knew what the age of the tubercle bacilli and the age of the lesion were when we started. This was not like the human lesion in which you could not tell whether the organisms had been there ten years or twenty years. We found that we could not recover tubercle bacilli from some of them. From some of the lesions we were able to recover susceptible tubercle bacilli (these were persisters); and in others we found isoniazid-resistant catalase-negative organisms that would not produce disease in animals; and in some we found isoniazid-resistant catalase-negative organisms that would produce disease.

We have duplicated in the experimental animal practically all of the phenomena that are observed in the human being, and there is no way of predicting at present, as far as I can see, whether drug therapy in a host is going to bring about negative bacteriology.

We have performed another experiment which I think is very important as far as persistence of organisms is concerned. We inoculated some guinea pigs in an experiment designed to go on for three years. We took large numbers of guinea pigs and produced caseous nodules subcutaneously in the testes. We used the testis because it is a local organ in which caseous lesions would remain and because we could remove a testis and leave one testis in. In some animals we produced caseous lesions in both sides.

Then we made smears. We inoculated with two different groups of organisms: one with H37Ra, which is an avirulent organism, and the other with heat-killed H37Rv. Every two months for a period of three years we used animals from these two groups, the ones inoculated with the heat-killed and the living Ra organisms. With the heat-killed organisms we made smears to see whether there was a diminution in the population.

Naturally, these organisms were just like a boiled egg in that the proteins were coagulated. Then what happened was different from what was happening in the body. However, these organisms even in the body still remain stainable acid-fast organisms for three years. With the H37Ra, which was a living attenuated organism, the population gradually decreased; but up to three years we are still able to see stainable organisms and occasionally we can recover one by culture. So it does show that these organisms can remain in the body in a dead stage or in a living stage for long periods of time and still remain stainable.

Dr. Middlebrook: Before we get into a discussion of recoverability from insult, whether by antimicrobial agent or host agencies, I would like to continue a little bit longer on this problem of modification of host immunity.

Dr. Robson alluded to this in relation to his experimental model, and we should discuss the chances of relapse from the theoretic viewpoint before the surgeons discuss what they think they can achieve by removing lesions from the lungs.

There is one aspect of this problem which, in my opinion, has been underestimated and that is that antimicrobial agents, such as isoniazid and streptomycin, have sterilizing activity only for multiplying tubercle bacilli. I wonder if there is any experimental evidence that the methods which have been employed in an attempt to cause such a decrease in host susceptibility so as to cause relapse in experimental animals might not be useful during intensive combined drug treatment to prevent organisms from going into such a state as persistence or latency.

Dr. McDermott, I think some studies have been done in attempts to cause relapse in mice.

Dr. McDermott: Yes, two things. First, we have not been able to reawaken these persisters by the administration of cortisone and a number of other duress types of activity that might be expected to produce relapse and that should affect host defenses. This is what makes me think we have a third force here, namely, that, independent of host immunity or the disappearance of drugs from the tissue environment, an independent action on the part of the parasite may be required before relapse can occur.

With respect to the other part of your question,

Dr. Middlebrook: In one or two experiments, we have been unable, when we gave cortisone, to produce the latent infection with pyrazinamide and isoniazid, and the tubercle bacilli failed to disappear. When we give cortisone in that situation, we do not prevent the antimicrobial action of the pyrazinamide and the isoniazid in that the populations fall at the same rate that they always do. However, you are quite right; we do fail to induce latency in that situation. In other words, the populations fall way down, but they do not go into a latent stage or at least do not do it uniformly.

Dr. Middlebrook: This suggests a possibility of avoiding latency.

Dr. McDermott: Yes. I had never looked at it in that way until you just mentioned it, but what you say is quite true.

Dr. Middlebrook: Actually, in clinical application, this was the purpose of avoiding those modalities of treatment and approach to other aspects of treatment which might interfere with the sterilizing activity of antimicrobial agents which have been applied clinically at National Jewish Hospital. The result has been that there have been few relapses, and only one indeed (which is a late relapse) due to drug-susceptible tubercle bacilli, out of 153 consecutively treated patients on combined drug therapy. This is why I emphasized my opinion, which was shared by Dr. Steele, that usually (in one case out of 153), relapse is initiated by drug-susceptible organisms.

The surgeons are often called upon by the physicians to do something about patients. Certain surgeons have been called upon to do something about patients and have been very willing to do so in the second or third month of treatment. When the physician felt that he could anticipate that his antimicrobial therapy, with or without bed rest and other methods of medical treatment, might fairly be expected to fail, he has called upon the surgeon to remove the gross cavitary lesion, which we agree with Dr. Auerbach is usually the source of relapse.

Is this a common practice today? Is this being done, for example, in Norway, Dr. Semb?

Dr. Semb: We have a minimum of preoperative medical treatment of four to six months (more likely six than four) and, if resection is considered to be the right type of treatment, then usually longer because we require a long period of chemotherapy to avoid complications after resection.

Dr. Middlebrook: Dr. Wilson, is this practiced in Boston?

Dr. Wilson: As you know—and I am sure that is the reason you asked me this—we feel directly opposite to this and we have no hesitancy at all in proceeding with surgery providing the clinician and the team working together feel that it is necessary. We are not advocating premature surgery but, once it is decided that the patient is going to require surgery, we think that you can proceed at any time providing you have so-called surgical criteria present. That is extremely important.

I think if you are going to apply surgery, then not only drug criteria but surgical criteria must be present. We are going to go into that tomorrow, but, roughly, the surgical criteria are that the lesion is in the unit of lung you want to resect; other areas are under control; and primary drug treatment is in effect. We feel then you can go ahead safely any time. Our complications are inversely proportional to the duration of preoperative chemotherapy.

Dr. Middlebrook: Dr. Davidson, what is your practice?

Dr. Davidson: At Sea View Hospital very few patients, if any, have been operated on before the termination of six months of therapy. I feel, however, the positive sputum and the presence of a cavity are synonymous. In other words, the cavity, as Carl Vishell stated, is a ledge upon which we come to grief and I think we must know still more about resistant organisms and susceptible organisms to evaluate the type of therapy which we perform.

Dr. Middlebrook: Dr. Chamberlain?

Dr. Chamberlain: This is a very interesting point. I have had the fortunate opportunity of working in two different environments in which the staffs have taken two different attitudes. For example, at St. Albans Naval Hospital, which is an active service in the Navy, the regulation from Washington is that the patient must be under surgical therapy within four months or he is discharged from the service and cared for by the Veterans Administration.

On the other hand, working with the Veterans Administration, the policy laid down in Washington would imply that the patient should be treated at least six months and perhaps longer, if I am stating this recommendation relatively accurately. Interestingly enough, in these two environments we are treating almost identical

patients, male population, ages the same, and so forth. We are treating the patients at St. Albans relatively early surgically and at the Veterans Hospital, after they have reached what was described as the target point. The results and complications in the two environments are almost identical.

DR. MIDDLEBROOK: Mr. Edwards, do you practice similarly in the United Kingdom?

MR. EDWARDS: I think it is true for me to say that in the United Kingdom six months is probably the minimum of treatment before we undertake surgery. We ourselves would take even a longer period than that; I think six months would be the very minimum. We would even give as long as nine months or a year of chemotherapy before we would undertake surgery nowadays with resection.

One of the bases of that is the histologic appearance in relation to the divided bronchus. We found in the earlier cases that there was a greatly increased evidence of tuberculous disease at the divided bronchial level, which we felt would add to the possible dangers of fistulae, and what have you, if we operated at that stage; so we tended to work at the later period. We have felt that resection should be the very last line of treatment after chemotherapy.

DR. MIDDLEBROOK: Is it because, as Dr. John Crofton puts it, in the United Kingdom they have a great deal of confidence in antimicrobial chemotherapy; or is it because you believe there is no opportunity for the surgeon to offer something to reduce the numbers of bacterial cells that Dr. Canetti talks about, and therefore to reduce the incidence of latency or of persistence of drug-susceptible or drug-resistant organisms?

MR. EDWARDS: I think we have very great confidence in antibacterial therapy, but one of the troubles in our particular hospital is that they always seem to be running Medical Research Council trials on chemotherapy and we never seem to get a chance to do surgery on the patients.

DR. MIDDLEBROOK: Very much like the Veterans Administration hospitals.

Dr. Steele, could you tell us about the Veterans Administration?

DR. STEELE: I think the Veterans Administration has been a little bit maligned, particularly by Dr. Chamberlain! Actually, the end point for observation of chemotherapy was reduced just so that surgery could be done earlier. The end point now is six months, and anyone is free to resect prior to six months and throw that patient out of the study if they think it is for the benefit of the patient. Personally, I don't think that I can predict the way Norman Wilson can the effect of chemotherapy at two months. I think there are certain cases which are obviously somewhat chronic and have quite a bit of productive disease that possibly can be resected at two months. However, I think that, if a patient comes in with a fresh lesion, with considerable exudative component in it, you have got to wait for six months before you can predict whether surgery is going to be necessary for that patient.

DR. MIDDLEBROOK: It seems that there are some groups that actually do practice early resection perhaps on the basis that they can anticipate, or feel that they can anticipate, that certain types of cavitary lesions are less effectively treated with antimicrobial therapy than others, and they don't wish to be faced with problems of drug resistance. If, in fact, the agents of relapse are usually drug-resistant mutants, then do you believe, Dr. Auerbach, that there might be some place for early removal of cavities in patients who might not respond to treatment?

DR. AUERBACH: If you follow the course of chemotherapy in the patients who have pulmonary tuberculosis, I think you will find that it runs along these lines: If the patient's onset of disease is very quickly followed by chemotherapy, there is a rapid closure of the tuberculous cavity, the patient will be treated medically, and the closure will occur within a month or two months after the chemotherapy has been instituted. Really, in these cases it makes very little difference what form of chemotherapy you give.

These are the patients who, when they heal, heal with closure of the cavity, inspissation of the necrotic contents, and in time calcification of those necrotic contents. On the other hand, if the interval between the onset of disease and the institution of chemotherapy is long, three, four, five, six, or seven months, and a cavity has been formed and the cavity has a thick wall, you will find that those patients are very difficult as far as therapy is concerned. If you follow these patients you will note that they fall into several categories. There is a group with which the medical men are easily discouraged; these patients are treated surgically. The lesions are removed after a short course of chemotherapy. I think these are

the largest surgically treated group. These are the cases also in which there is the greatest number of failures chemotherapeutically. If chemotherapy is successful, it is in this group that the greatest incidence of open-healing is seen. In other words, these are the patients with thick-walled cavities in whom it is difficult for the cavity to collapse because of the amount of fibrosis. They will fall into the category of unsuccessfully treated patients, or, if successfully treated, the majority will recover by "open-healing."

In answer to your question, I would say that in this latter group you would find, in my opinion, the greatest indication for surgery.

DR. MIDDLEBROOK: Either early or late.

DR. AUERBACH: Early or late, yes.

DR. MIDDLEBROOK: There are bacteriologic problems associated with the definition of relapse, as we have already discussed them. There are problems upon which we cannot agree perhaps because of lack of the development of our technology or perhaps because tubercle bacilli can multiply in tissues without passage into a bronchus. This, therefore, makes it impossible for us, at least for a period of time, to identify the illness of the patient, i.e., the roentgenographic change or change in the patient as being caused by tubercle bacilli.

We have talked throughout this symposium thus far about tubercle bacilli as if they were quite uniform fellows—we are quite willing to use the term "the tubercle bacillus" as we would use "the man." There are obviously many variations among strains of tubercle bacilli, however, and, in many institutions in this country, 2 or 3 per cent of patients admitted (outside of the South) are not excreting organisms that can be called typical tubercle bacilli. Yet, from a clinical standpoint (not necessarily from an epidemiologic standpoint), these patients are diagnosed as having tuberculosis. They may respond to the combination of treatment which the particular clinicians involved might apply, but they are apparently more difficult to treat originally. Furthermore, they come under this group of patients who may respond at first, but "relapse."

Inasmuch as there is no such thing as "the tubercle bacillus," and actually in practice if one is concerned with tuberculosis one is really concerned with pulmonary Mycobacteriaceae, I would like to ask Dr. Forman to discuss some of his studies on the different types of mycobacteria which can be agents of pulmonary disease, tuberculosis or diseases simulating tuberculosis.

DR. FORMAN: There are several types of mycobacteria to be considered here. The first major group is the group commonly referred to as the atypical acid-fast bacilli, or the anonymous mycobacteria. We have several varieties among these that are referred to as the photochromogens, the scotochromogens, and the so-called nonpigmented varieties or the Battey types. These will produce cavitary disease clinically, roentgenographically, and histopathologically indistinguishable from true tuberculosis.

As Dr. Middlebrook intimated, these are much more difficult to treat since they do manifest more resistance to the antituberculous drugs presently being used; and in some of the cases that you might encounter that don't respond quite readily that you feel should respond, I think it would be very wise to check with the laboratory that you are dealing with to make sure that what they are reporting as a tubercle bacillus is actually a true tubercle bacillus and not one of these atypicals.

These atypicals in general can readily be distinguished from the true tubercle bacillus. However, many laboratories are not aware of this, and are not aware of the newer techniques in tuberculosis bacteriology. It is absolutely urgent that laboratories in general become aware of these techniques. In general, these acid-fast bacilli grow intermediately between the rapid growers and the true tubercle bacilli, and should be readily distinguished by the technician. We will not go into the bacteriology here. I don't think this is the place for it.

However, there is one other class of acid-fast bacilli that needs some consideration and I think has been entirely overlooked, some of the rapidly growing strains. I am referring particularly to the species of mycobacteria referred to as *Mycobacterium fortuitum* which may also produce cavitary disease. We have had one instance at our hospital, at Olive View, in which this very rapidly growing strain, which appeared within twenty-four to forty-eight hours after inoculation, produced cavitary disease in this one individual. We could not obtain a tubercle bacillus or anything else that could possibly account for the infection.

This patient died. On autopsy the only organ-

ism we could recover was this particular strain of *M. fortuitum*, and according to Dr. Bogen, the condition was tuberculosis histopathologically.

DR. MIDDLEBROOK: In such cases there are some surgical groups, I know, who feel that surgery is indicated earlier during the course of therapy, especially if there is an opportunity to affect the bacterial population at all by antimicrobial chemotherapy. The policy is to resect the gross cavitary lesion within a matter of four to eight weeks after initiation of chemotherapy.

What do the surgeons believe? How do the surgeons believe they affect the rate of relapse from tuberculosis by applying surgery? There are communications in the literature which tend to indicate that the relapse rate is the same whether or not surgery is performed, even in control studies where there was purely chance selection as to which patients would receive surgery and which would not receive surgery.

Do the surgeons believe that, in patients who have been sputum negative, have reached the so-called target point (if I may use that term), they modify the chances of relapse by removing lesions, and what types of lesions from physiologic or roentgenographic characteristics would lead the surgeons as guides in their decisions?

Dr. Steele, would you initiate the discussion, please?

DR. STEELE: Of course, that is a pretty complicated question. I assume, in the first place, you are talking about closed lesions and then also possibly open-negative cavities. Of course, we can leave out the frankly positive open cavity. As far as closed lesions are concerned, we would like to think that we are preventing relapse. I don't know that we actually have any statistical proof at the moment.

As far as open-negative lesions go, there is a lot of loose talk about open-negative cavities and some surgeons believe that you shouldn't operate on them if they have been negative over a year, but from a practical standpoint you aren't faced with that question. You are faced with a patient with a cavity, say, at six months, and he may have converted his secretions in the meantime, so that actually you really don't know whether you are operating on an open-positive or on an open-negative cavity most of the time.

As I say, then, from the cavitary standpoint, from a practical standpoint, if we are faced with it in a patient at six months, we just have to operate.

DR. MIDDLEBROOK: Mr. Edwards?

MR. EDWARDS: Yes, I think that is really the only reason why we can justify our existence in these cases, the hope that we are doing better than nature or the physician. We did operate some years ago on a large number of caseous nodules in the hope that we were doing some good, but I think the pathologic changes in those under increased chemotherapy has probably altered the view. I think that any very large caseous nodules, such as something over 2.5 centimeters, is probably something that we should remove.

We are really now getting a little on to our subject of tomorrow, and I don't think we should pursue this too deeply now.

DR. MIDDLEBROOK: Dr. Epstein, do you believe that the medical man has something to offer in the way of continued drug treatment over long periods of time rather than risk the morbidity and possible mortality of surgery in a patient who is sputum negative, whether there are residual closed lesions or so-called healed open cavities in patients?

DR. EPSTEIN: We have listened to the surgeons and I have no argument with them. Certainly, if a lesion is localized to one side and the patient is a good surgical risk, there is no argument about the removal of that particular portion of the lung.

Unfortunately, that is not always so. Our hospitals are now filled with these chronic cases that are resistant to isoniazid, streptomycin, and PAS. We have been very fortunate in the past five years in studying these chronic resistant cases and, as you people know, we have been using several treatment modalities. We have been using principally the drug called cycloserine or seromycin,® and we have been very, very impressed by this drug.

At first we got into a little bit of trouble; for one reason or another we got into trouble with toxicity and we have had some neurotoxic symptoms. We haven't found as many as some have reported and, to my amazement and gratification, the reactions haven't been reported any more and those who have been reporting them are repeating treatment in the same cases as before.

Since 1954 we have used several regimens. We

have used cycloserine alone in one-gram doses, and we have gotten neurotoxicity; but the results weren't very bad and we have been able to salvage a good number of cases. At no time did we neglect surgical treatment because of our experimentation.

Then we reduced the cycloserine dose to a half gram. We didn't have any toxicity, but the results weren't as good although they were, in a way, gratifying. This was particularly the case when we were handling people who would have been dead in a year or two because of a terrific number of pathologic lesions.

Then we combined cycloserine with isoniazid, and we were amazed because experimentally, as Dr. L. H. Schmidt has shown, it is a good combination. Experimentally in monkeys, as you know, he has shown rapid resolution in the monkeys so that there weren't any residuals left in experimental tuberculosis.

Then we wondered why we were getting neurotoxicity and why we couldn't increase the dose. So we increased the dose to two grams and, of course, we got a little toxicity, but we were able to control the toxicity very easily with pyridoxine. Two grams of cycloserine are more effective than the half gram or one gram.

Now we have a series of patients whom we have started to treat with two grams, with pyridoxine simultaneously. This is going to be reported very shortly; I saw the proofs of the paper a little while ago.

Why do we allow these cases to get so bad? Isn't there something we could do to avoid the tremendous holes in the lungs that we see? Recently we have had a series of cases in which we started small doses of steroids after four months of treatment.

DR. MIDDLEBROOK: Of original treatment?

DR. EPSTEIN: Original treatment cases. We were able to collect twenty-one patients in whom we have started isoniazid, streptomycin, PAS, isoniazid and PAS, or cycloserine and isoniazid; and at the end of four months we were not satisfied that the improvement was adequate. We added small doses of steroids, and in this instance we added 10 milligrams of Meticorten® a day. In all but one case we had rapid resolution and conversion of sputum. All of these patients had had positive sputum at the end of four months, so it made us think: "Shall we try to cure the case before it becomes so bad?"

DR. MIDDLEBROOK: I am sure, Dr. Epstein, that we would all agree it is important to continue the investigation of original treatment cases; what we have been discussing are problems of relapse. There is one more aspect of the problem of relapse which I don't believe we should omit, and that is the problem of the claims of inhibition of relapse by continued administration of one drug, namely, isoniazid.

Dr. Raleigh, would you like to introduce the discussion of this subject?

DR. RALEIGH: Certainly, in a patient whose organisms were susceptible to isoniazid it seems reasonable that the continued administration of this drug would continue to suppress the multiplication of these organisms and prevent relapse. Our experience, however, is not quite as comforting as this, even in the more favorable cases. By that I mean relapses in closed-negative cases, target-point cases, are just as likely to occur while the drugs are still being given as they are to occur after the drugs have been stopped.

In other words, the time of relapse is usually within the first twelve to eighteen months of continued therapy, and the number of relapses that occur after the discontinuation of therapy is strung out over the next three years. I don't mean that, if we continued the drugs into the third and the fourth and the fifth years, we might not prevent an additional fraction of those late relapses. We might. But the fact that so many of the relapses take place while therapy is actually under way makes me doubt that any substantial number of late relapses will be prevented by the administration of isoniazid or any other combination of drugs that I know about.

DR. MIDDLEBROOK: Then you believe that certainly the pattern of relapse, or the curve of relapse, will be the same or is the same today at least as it was in the pre-antimicrobial era?

DR. RALEIGH: So far it appears the same. The incidence of relapse during the first year after the achievement of certain therapeutic objectives, that is, in the closed-negative stage or even open-negative stage, goes up sharply. About 60 per cent of those relapses that will occur in five years have already occurred within the first year; about 85 per cent will have occurred in two years; and the remaining 15 per cent are scattered over the third, fourth, and fifth years.

I don't think that chemotherapy has altered

the pattern of relapse very much except to depress it generally. I don't think we can take any comfort in the fact—or take any discouragement from the fact—that perhaps chemotherapy is only postponing relapses and that the patients will all relapse later anyway. I think the curve of relapse is the same as it was in the days of bed rest, pneumothorax, pneumoperitoneum, and other therapeutic programs; and I don't think that the continuation of therapy alone is going to make a major dent in this curve. I think it may eliminate a few scattered relapses.

DR. MIDDLEBROOK: We started this discussion with a consideration of the relationship between the healed tuberculous lesion of today (healed on antimicrobial therapy, on the one hand) and the tuberculous lesion which was not healed by chemotherapy but rather by methods that were available to us in the pre-antimicrobial era. Would you anticipate from your very extensive experience in anatomic pathology, Dr. Auerbach, that there should be no difference in the pattern of relapse, when all chemotherapy is discontinued, from your studies of anatomic specimens given to you by surgeons or through necropsy?

DR. AUERBACH: What I should like to know from Dr. Raleigh is what does he consider a relapse.

DR. MIDDLEBROOK: We finished that a long time ago. We couldn't agree on that.

DR. AUERBACH: Is it renewed activity in addition to the appearance of tubercle bacilli in the sputum? Are there new lesions?

DR. RALEIGH: It depends, Dr. Auerbach, on what group of cases you are talking about. In the closed-negative group, that is, in the target-point group, the relapses were in most cases merely the reappearance of tubercle bacilli in the sputum or gastric contents. The relapses in the "open-negative" cases were much more commonly a combination of unfavorable X-ray change and the reappearance of tubercle bacilli in the sputum. These were not by any means all single positive cultures with no further evidence of tuberculous activity. They were relapses, I think, which most of us would have taken seriously from a clinical point of view.

DR. MIDDLEBROOK: Do you take them seriously from an anatomic point of view?

DR. AUERBACH: That is why I wanted to get the definition of what Dr. Raleigh was talking about, because it does fit in with what we see anatomically and what we would expect. Under the influence of chemotherapy the cavity closes with inspissation and there is a patent bronchus. We do know that late liquefaction occurs, and it should not be surprising to us at all that necrotic material containing tubercle bacilli would be expectorated in the sputum and that, in spite of the fact that it is expectorated, no spread of the disease is found. So we would see the inspissated cavity, or partially inspissated cavity, the open bronchus, and failure of spread.

On the other hand, the open-negative cavity (and I think you can only call it an open-negative from a roentgenographic point of view) is one which has a fairly thick wall and may or may not have necrotic material along its inner wall. I think the microbiologists have found that it is much easier to grow tubercle bacilli out of these lesions than from the inspissated cavity. Therefore, if this necrotic material got into the bronchus and into the bronchi, I would expect more spread. So I think the changes that were described by Dr. Raleigh are what we would expect post chemotherapy anatomically.

DR. MIDDLEBROOK: Essentially no different from the pre-antimicrobial pattern of relapse.

Dr. Chapman, you do follow a large number of patients in Detroit. Is the pattern essentially the same as Dr. Raleigh described it in his experience?

DR. CHAPMAN: Our experience in this regard is almost identical with Dr. Raleigh's, that the pattern of relapse follows this course. About two-thirds of the patients with relapses whom we have observed have ultimately recovered, mostly through the institution of surgical treatment as a corrective rather than through recourse to other successful drug therapies. The reason is that many of the cases, I think, took a long time to reach target point, were rather tenuously held there, and maybe surgical treatment was passed over.

If, on the other hand, a patient who has surgery has a relapse, his recovery rate is not so high. We have already squandered most of our chances, I think. We have nothing much left. I think, though, that the major problem of relapse is solved by surgery.

DR. MIDDLEBROOK: Dr. Chaves, in your New York experience, is the relapse rate after discontinuation of chemotherapy by patients in the

health clinics about the same as it was in the pre-antimicrobial era?

DR. CHAVES: I think there has been a very dramatic fall in the number of reactivations we see. This is, I think, very striking in the clinic and in the number of patients referred for re-admission into the hospital. But I believe that Dr. Raleigh was referring to the pattern of relapse rather than the actual number.

DR. RALEIGH: Yes, the time of occurrence. The number is certainly much lower.

DR. CHAVES: There is one pattern of relapse that we do see that may not show up statistically. I have a clinical impression that in a number of instances, more than coincidentally there is rather promptly a relapse with the discontinuation of chemotherapy. I wonder whether this is a clinical impression that I have alone or whether other clinics have observed the same pattern.

DR. MIDDLEBROOK: Dr. Julia Jones, what is your clinical impression?

DR. JONES: Mine is very much the same as Dr. Chaves' although I don't have as clear an impression that relapses occur on cessation of therapy. The actual thing that impresses me most is that we see so few relapses of any kind. I had occasion a year or so ago to review our re-treatment cases and I was quite impressed by the fact that very few of that group were really relapses. They were people who had been mis-judged clinically or the familiar group who wander around and never get cured, but over-ail, as Dr. Chaves said, an impressive drop is the thing that strikes me.

DR. MIDDLEBROOK: Dr. Tuttle, do you believe that the surgeon plays a role in the prevention of relapse from tuberculosis?

DR. TUTTLE: I certainly do. I believe that a fairly large percentage of lesions which are removed surgically do have at least stainable organisms within the specimen. Despite the fact that a patient has been under a long period of antimicrobial therapy, the fact that the organisms won't grow is just because they are more or less sterile. But even a sterile human being can get into a lot of trouble or cause a lot of trouble, and I feel that also maybe a sterile tubercle bacillus can cause a lot of trouble, too.

I believe that our modern concept of reducing the lesion to a certain point and then removing it is better than leaving it there to fester. They will fester in time.

DR. MIDDLEBROOK: Dr. Burke, relapse occurs, I presume, in our sister to the north.

DR. BURKE: Oh, yes, we have relapse problems in Canada, but it was Dr. Froman's remark that made me feel that I should bring a little something to the attention of the panel.

About three years ago our bacteriologist, Dr. Mankowitz, developed an improved method for detecting tubercle bacilli on culture media. We have found, as a result of using this technique, that we can detect tubercle bacilli in the sputum or in specimens of a number of people who are classified normally as "open-negative." I am not going to say very much about that, but I do want to point out that we picked up in the last two years 150 atypical strains of tubercle bacilli, atypical acid-fast bacilli. Some of them are very interesting ones in that they behave much as true tubercle bacilli do. Others are intermediate even all the way down to saprophytes; and with our precipitation techniques, it is possible to separate these organisms out.

I think that these organisms sometimes found in people who we know really have active tuberculosis are very important ones to follow, and some attention should be given to trying to sort out these atypical bacilli stirred up in people who presumably have tuberculosis as well as possibly other diseases.

DR. MIDDLEBROOK: I think all of us would agree that the definition of the term "relapse" and the use of that term in practice depends, to a large extent, though perhaps not exclusively, upon the technology of the bacteriologist. Therefore, I would like to ask you, Dr. Steenken, whether you anticipate any great improvement in our technology of bacteriologic investigation either of pathologic materials in excreta, secreta, or in the tissues themselves during the next few years?

DR. STEENKEN: I would hate to say I wouldn't anticipate because I hope that everybody is going to continue working. I would like to say, however, from my experience in having tried all available techniques for culturing the tubercle bacillus, that there is no one method that is a hundred per cent reliable for cultivating tubercle bacilli, even from some of the lesions that contain millions of organisms.

If you use all of the techniques available you will gain a few more positive bacilli; and if you use the same one technique over and over again,

you will always gain a few more positive results. I don't think there is any absolute technique for recovering tubercle bacilli. Maybe you do, Dr. Middlebrook.

DR. MIDDLEBROOK: I prefer not to discuss it.

Dr. Canetti, Dr. Tuttle made a very interesting point, it seems to me, namely, that tubercle bacilli which are sterile and are presumed to remain sterile, in the sense that they are unable subsequently to reproduce their kind, are still things that ought to be taken out of the human body. Do you believe that there is any anatomic evidence to justify this point of view, or bacteriologic evidence?

DR. CANETTI: Frankly, I am afraid I don't know about any such evidence. They might be harmful. If we want to take out all nonviable bacilli which exist in the case of healed tuberculosis, I think many patients should undergo very extensive surgery. In any cured tuberculosis, lots of nonviable bacilli exist, in my opinion; and we have to wait until they disappear, until they disintegrate. They are perhaps harmful in a certain way of toxicity, but, frankly, I don't see how.

DR. MIDDLEBROOK: There is one final problem of relapse which faces us all. Is there any patient who has had clinical tuberculosis, especially the patient who has had advanced serious clinical tuberculosis, who is not a susceptible host? What would members of the panel suggest as to the prevention not of relapse from endogenous tubercle bacilli, but from the possibility of exogenous reinfection? In the first place, does any member of the panel believe that exogenous reinfection is possible many months after all of the evidences of successful chemotherapy have been provided? Does any member of the panel think that there may be a problem of protection of such persons by some means or other from exogenous reinfection?

MR. EDWARDS: This is a very difficult problem. One wonders when the patient is sent back after surgical treatment, perhaps to a household in which his wife is also tuberculous (and maybe other members of the household as well), and the original patient whom you have operated on returns in a year's time with the recurrence of the disease—you just wonder whether, in fact, an exogenous reinfection has occurred in that patient.

My impression is, that, when a patient has had disease for that length of time, has gone through a course of treatment, probably his resistance is so high that the likelihood of his getting an exogenous infection (at any rate, for a long period of time) is very remote.

DR. MIDDLEBROOK: Dr. Raleigh?

DR. RALEIGH: I think that the only method I know of by which either exogenous or endogenous reinfection might be prevented or the incidence of it reduced would be by continuous long-term chemotherapy. I have already said that I think the number of relapses that would be prevented that way is rather small.

If you are interested for a very special reason in preventing a relapse in a special individual, a special group of individuals, I think this might be worth investigating; but I don't think that as a general program the proceeds are likely to be great enough to justify the trouble and the risk and the expense.

DR. MIDDLEBROOK: Dr. Robson, do your experimental studies provide any suggestions to you on this point?

DR. ROBSON: I am afraid my experiments don't, but I would like to take this opportunity to make one very, very tentative point. We do usually regard treatment of tuberculosis as continued chemotherapy until certain results have been achieved. As far as I know, no one has ever considered giving chemotherapy for periods of, shall we say, three months and a month of no drugs in between, and then going on with chemotherapy again, and so on, the idea being that you would allow immunity to remain. It isn't only a question of the number of bacilli there, but the fact that we have some evidence that treatment with chemotherapeutic agents does decrease the immunogenic properties of tubercle bacilli. I think that needs further investigation; but, if these things are true, then we may have to consider the possibility of giving chemotherapy in that way. If it wasn't so late in the session I would very much like to consider this question.

DR. MIDDLEBROOK: Dr. Steenken?

DR. STEENKEN: I certainly do believe in exogenous reinfection both in humans and in the experimental animal. However, the incidence I am not too certain of; but in guinea pigs you can easily tell that. Again, the important thing, as far as exogenous reinfection goes, is the number of organisms the patient comes in contact with

and how he comes in contact with them. As you all know, it is droplet infection that really causes disease. Yesterday, in comparing Dr. Middlebrook's work with Dr. Schmidt's, we found the comparison wasn't too valid because Dr. Middlebrook is using an atomized inhalation in small droplet form, but Dr. Schmidt is using intratracheal infection in a large amount; and many of the organisms are coughed out by the monkey, whereas, with the droplet, there are many sites for infection to take place.

DR. MIDDLEBROOK: Dr. Steele, do you see any problem in this? Do you see any problem that you should be concerned with clinically?

DR. STEELE: Clinically I think it is pretty late to start to discuss this, but such matters as rehabilitation may be important in the prevention of relapse, just as important as biologic considerations.

DR. MIDDLEBROOK: This is the prevention of exogenous reinfection, if it is a problem.

DR. FROMAN: I don't think I have too much to add to this, but we did have one incidence of exogenous reinfection in a technician who was a former patient, and he was found to be infected by a streptomycin-resistant tubercle bacillus used during an experiment.

DR. AUERBACH: In post-chemotherapy cases it is a very difficult thing to prove anatomically, because one could say that the new lesion occurring on the opposite side might have been there prior to therapy or might have come from another site. But in the era prior to chemotherapy, when we used to see cavity closures under one of the forms of collapse therapy, we would occasionally see patients come back to the hospital ten or twelve years later with a new disease on the opposite side. Then, having the opportunity to examine both lungs at that time, we would see that the lesions of the old disease were healed and that new disease, unrelated to the old, was present on the opposite side. I will say that both the evidence today and in pre-chemotherapy days is that new exogenous disease in persons developing tuberculosis is very infrequent indeed.

DR. MIDDLEBROOK: You think it might not be more frequent today with chemotherapy than in the pre-chemotherapy era?

DR. AUERBACH: I can see no difference, although it is very hard to say because the material is not comparable.

DR. EPSTEIN: We see that this problem exists. As long as boys and girls will get together, there will be this problem. We find that perfectly healed persons will mix with those with open cases of tuberculosis and develop tuberculosis all over again. Of course, the problem is what to do about it, and I really am bewildered as far as that is concerned because we can't give everybody isoniazid or any other drug for the remainder of their lives.

DR. MIDDLEBROOK: Why not?

DR. D'Esopo, you are interested in exogenous reinfection.

DR. D'ESOPO: I would like to submit the suggestion that exogenous reinfection might become really quite important if our chemotherapy really became effective, particularly if we got bactericidal drugs. For example, I believe reinfection in syphilis is much more important since we have had penicillin than it was in the prolonged chemotherapy of syphilis.

DR. MIDDLEBROOK: You distinguish between the activity of penicillin against *Treponema pallidum* and isoniazid against tubercle bacilli.

Dr. McDermott, do you distinguish between those two?

DR. MCDERMOTT: No.

DR. MIDDLEBROOK: This seems to me to have been a fascinating session because essentially what happened is that we have elicited differences of opinion. These differences of opinion may well, in my opinion, be based either upon my being ignorant, for example, of what B knows, or it could be that we have entirely different ways of looking at life in general. I suggest that it might be the latter, for example, in the preoccupation with the problems of exogenous reinfection, because this includes psychologic, sociologic, and cultural problems.

So far as the mode of action of antimicrobial agents is concerned, it would seem there would be less room for this sort of complication.

There is only one thing that I would like to say in summarizing our experience, rather than trying to summarize all of the problems which have been presented, and that is that there seems to be some agreement that human beings with pulmonary tuberculosis can be treated to a large extent effectively with antimicrobial agents. The surgeons and their collaborating physicians feel that excision of certain types of lesions is indi-

cated and that, along with the early manifestations of effectiveness of antimicrobial chemotherapy, there is a decrease in the number of relapses, whether these relapses be endogenous, as they probably mostly are, or exogenous. They also believe that the patterns of relapse, at the present time at any rate, with the present modalities of therapy medically and surgically, seem to be very similar to the patterns of relapse in the pre-antimicrobial days.

I would like to leave the panel with only one suggestion, namely, that there are perhaps within the field of the problems of original treatment and the success of original treatment, problems which have relevance to the avoidance of relapse. These problems I believe are at such a level of experimental and theoretic consideration that they are really beyond the range of our discussion this morning.

Thank you.

PANEL FOUR

Panel members, left to right: PHILIP D'ARCY HART, JULIA M. JONES, PAUL T. CHAPMAN, KATHARINE R. BOUCOT, MICHAEL L. FURCOLOW, FLOYD M. FELDMANN, GEORGE N. J. SOMMER, JR., THEODORE L. BADGER

PANEL FOUR

TUBERCULOSIS CASE FINDING: THE PROBLEM IN THE GENERAL POPULATION, SCHOOLS, AND HOSPITALS

Chairman: KATHARINE R. BOUCOT
Introducer: THEODORE L. BADGER
Panelists: PAUL T. CHAPMAN
FLOYD M. FELDMANN
MICHAEL L. FURCOLOW
PHILIP D'ARCY HART
JULIA M. JONES
GEORGE N. J. SOMMER, JR.

DR. BOUCOT: It seemed to me that case finding should have started off this symposium but, after having heard Panel One, it looks as though we are in a better position with this location on the program than we would have been if we had started it off, because certain areas were defined for therapy which make it extremely important for case finding to be correlated with the treatment of reactors. During this discussion we will touch upon most of them.

Dr. Boucot introduced the members of the panel:

Dr. George N. J. Sommer, Jr., a thoracic surgeon and, very unusually, interested in tuberculosis in New Jersey State Hospital, a mental institution, where he is Attending Physician in Tuberculosis.

Dr. Floyd Feldmann, the Medical Director of the National Tuberculosis Association and Director of Medical Research for the American Trudeau Society.

Dr. Michael L. Furcolow, Associate Clinical Professor of Medicine at the University of Kansas School of Medicine, and Medical Director and Chief of the Kansas City Field Station of the Communicable Disease Center of the U. S. Public Health Service.

Dr. Theodore Badger, past President of the American Trudeau Society, and Assistant Clinical Professor of Medicine at Harvard Medical School and Visiting Physician at the Boston City Hospital.

Dr. Philip D'Arcy Hart, Director of Tuberculosis Research in the Medical Research Council of Great Britain.

Dr. Julia Jones, Assistant Clinical Professor of Medicine at the College of Physicians and Surgeons at Columbia University, and Visiting Physician of the Chest Service at Bellevue Hospital.

Dr. Paul T. Chapman, Assistant Clinical Professor of Medicine at Wayne State University School of Medicine, Tuberculosis Controller for the City of Detroit, and Director of the Tuberculosis Division of Herman Kiefer Hospital in Detroit.

The Chairman, Dr. Boucot, is Professor of Preventive Medicine and Clinical Professor of Medicine, Womans' Medical College of Pennsylvania; Physician, Womans' Medical College Hospital of Pennsylvania, Philadelphia.

DR. BOUCOT: We are fortunate to have Dr. Badger as our Introducer, and we will turn at once to him.

DR. BADGER: I also am really not quite sure what the Introducer is supposed to do except as I have been tutored by Dr. Boucot, and I will try to bring us up to date on some of the problems in tuberculosis.

I think that any discussion of case finding in tuberculosis deserves the question: Does a tuberculosis problem exist? There is very little doubt in our minds about its existence in such places as Alaska, parts of South America, the Ryukyus Islands, the Far East, and the south end of my own city of Boston. In the United States, however, if one regards only the death rate, there is reason to be led astray in one's thinking.

Briefly bringing us up to date about the nation as a whole, I am indebted to Dr. Edward T. Blomquist for some of the figures for continental United States which he and his department very kindly supplied for me.

The death rate for 1956 was 8.4 per hundred thousand; and the new case rate, 41.2 per hundred thousand. This period, as all of you know well, is one in which the new cases over the past five or ten years have fallen off very slowly while the death rate has gone down very rapidly.

If one takes the death rate by broad age groups in the United States and speaks particularly of their percentage decline, it is of particular interest that, between 1936 and 1956, in those less than twenty-five years of age, the rate of decline

has been 96.7 per cent; between the ages of twenty-five and forty-four, 92 per cent; while the decline rate for those more than sixty-five has been 62.9 per cent.

If the tuberculosis death rate is compared—and this is one of the most interesting aspects—for those less than twenty-five, the death rate is 0.9 per hundred thousand; while for those more than sixty-five, the rate is 34.5 per hundred thousand.

There is another interesting slant in regard to the death rate by the size of cities. In large cities of 500,000 or more, the death rate for 1956 was 13.5 per hundred thousand, while it was 10.3 for cities of one hundred thousand to five hundred thousand. In such cities (100,000 or more population) 42 per cent of the total tuberculosis deaths occur. In other words, the large cities appear to have the increasingly acute problem; but elsewhere in the United States, outside the larger cities, the death rate is 6.8 per hundred thousand population. Fifty-eight per cent of the total tuberculosis cases come from areas outside the large cities in the United States.

Economically, across the country, tuberculosis still remains a considerable problem. In the United States, during 1952 the cost was 621 million dollars. The cost rose to 725 million dollars during 1956, a rise of more than 100 million dollars, indicating once again a very significant financial problem.

One other aspect of case finding that is of importance is that of deaths, new "active" cases, and known cases in that large reservoir of persons who need medical treatment; in other words, the mortality, the incidence, and the prevalence. Actually, in figures, the deaths amount to some 14,000, the new active cases to some 69,000, and the known cases needing medical supervision to some 400,000. This is a large reservoir of prevalence, in which two-thirds of these cases are "inactive" and approximately one-third of them are "active."

These figures point out a few of the areas where tuberculosis lies across the country today. Having established reasonably clearly that tuberculosis still is a problem of some magnitude, I think that probably the case-finding job is equally difficult. One might ask if there is any fixed pattern for case finding. I think experience does not bear this out particularly, and we are finding that what is good for the goose is not always good for the gander. In other words, techniques and methods of attack would vary greatly from one community and from one nation to another.

It is hard to find a common denominator of case-finding programs. I remember a number of years ago one of my early teachers in chest disease, Dr. Frederick T. Lord, made a rather useful observation that one had to go out and look for tuberculosis if one wanted to find it. Actually, this is the one common denominator today, the catalytic agent of any program, and certainly it is the core of any tuberculosis program whenever one is planned.

There are two important developments over the past fifteen years that have in one way or another rather seriously affected our tuberculosis case-finding programs: The first is the discovery of antituberculous drugs, thereby speedily lowering the death rate beyond all expectations; and, second, the winning of World War II with the atom bomb, thereby activating a fear of ionizing radiation even in the minuscule doses of a chest X-ray film. In spite of these innovations there remain two techniques that are really essential in any program: the tuberculin test and the chest X-ray.

There was a time in the "glamor" days, when tuberculosis death rates were high, when the control of this disease was perhaps a little bit more easily exemplified by the common occurrence of a death, and thereby immediately outlining an area of contact which was important. Today all of that is really fundamentally changed, and communities swarm with old cases and new cases that are sometimes extremely difficult to find.

In many areas of the country, as was brought out yesterday in the afternoon panel, approximately 50 per cent of active cases appear to be under treatment at home, and the distribution and follow-up of these is often extremely difficult. Probably more cases than ever of active and inactive tuberculosis are discharged into our communities, and it is of interest that in the New York state hospitals in 1945 there were only 301 total dischargees alive, and in 1957 nearly three times that number, or 859.

It is also of interest that during that period of time, from 1945 to 1957, as stated in the annual report of the New York state hospitals at the end of last year, 55 per cent of these cases were active in 1945, and 59 per cent in 1957. This is about the same number and not particularly significant

statistically, but this is a group of patients who are returned to their families and often to their solitary lodgings, many with open cavities discharging bacilli in all stages of activity and drug resistance.

I think little more need be said about the complexity of the problem. I think one of the most essential areas of case finding must be this large community reservoir, not only of new cases, but of an unknown number of patients whose disease will relapse and become a source of other new cases. This is really not an easy problem—total community prevalence of new and old cases. How shall we proceed? What plan shall we adopt? What techniques are most applicable?

In different geographic areas this is always a very different problem. On the east coast of Labrador, among the Eskimo and Montaignais Indians, the very high tuberculosis infection rate vitiates the usefulness of the tuberculin test. Up there Dr. William Paddon, working out of the Grenfell Mission Hospital in Northwest River, Labrador, has, since 1943, followed this problem pretty carefully. His technique has been simply that of taking 14- by 17-inch X-rays in a hospital ship which has gone around the coast and he has X-rayed practically everyone in all of their communities. No BCG has been used in this area. By this approach alone Dr. Paddon has watched the mortality fall from 400 per hundred thousand to 35 per hundred thousand between 1943 and 1956. New cases dropped from 25 per hundred to 4 per hundred during the same period of time.

In Houston, Texas, as in many other areas, tuberculin testing of school children is the preferred mode of case finding by Dr. Hsu, and the harvest has been rich in the finding of old open contacts or of new open contacts. In the poorer districts of Houston, 2.2 per cent of the children were reactors. This infection rate, though not remarkably high, has been unusually productive in revealing contact cases of open disease.

The reasons for this are not entirely clear. It may be the nature of the Mexican population in Houston and it may be due to other things, but they have had a very much higher incidence than most localities have had.

In Boston, on the contrary, the infection rate as shown by tuberculin reactivity among school children in high-incidence areas has been higher than in Houston; but the discovery of new open contact cases not already known has met with poor results. Dr. Kahn, Chief of the Division of Infectious Diseases of the City of Boston Health Department, with the help of the Boston Tuberculosis Association, has shown a rather interesting turn of events, not entirely explainable.

In the tuberculin testing program in high incidence areas among school children in 1957-1958, 13,900 tests were done and 792, or 5.69 per cent, were reactors. The difficult problem has been, however, to find new active cases from this group. Out of this has come the discouragingly low figure of only one new active adult case and one new active primary case. This is not as good as was hoped for and it may evoke some discussion from the panel.

On the other hand, it is of interest that, in these same areas, 70 per cent of the new active cases reported in Boston during the last three years have been reported from hospitals even without X-ray programs: in 1955, 71 per cent; in 1956, 68 per cent; in 1957, 73 per cent.

These are rather factual data in a way, and I think perhaps make us lean toward the need of routine general hospital admission X-ray programs in this area in addition to any tuberculin testing program.

These three widely divergent communities that I have mentioned indicate the varied usefulness of different techniques as far as case finding is concerned.

When do we use the tuberculin test and when the X-ray or both? This, I hope, the panel will take up in detail and I will, therefore, barely touch on it. I merely bring it to our attention and add that, because of the pressures exerted from interest in the effects of ionizing radiation, the tuberculin test is widely recommended for those in the younger age groups certainly, with a chest X-ray only for the positive reactors.

I think it is unwise to believe that tuberculin testing surveys will be cheaper than X-rays; nor should we consider that tuberculin testing programs will even be successful unless our public relations are considerably extended and improved. People must be taught the value of this test, not only for locating those with tuberculous infection, but in excluding those who are free from it. I think it is very important to recognize that the success of any program will depend primarily upon how much the public is impressed with its value before any local plan is put into effect.

Recently, in talking with Dr. Weidman about this matter in the western part of Massachusetts, where there had been some antipathy to the test, he felt that public education had resulted in so large a number applying for tuberculin tests (aside from captive audiences like school children) that there were really more than they could handle. I think he has demonstrated that public relations has done a job.

What about general hospital X-ray admission programs? I thought it might be of interest to have here the age distribution of patients in general hospitals on what is recorded as "day of reporting" in 1953 in continental United States. These are rather interesting figures, as a matter of fact, and they were assembled by Dr. Frank Dickinson, Director of the Bureau of Medical Economic Research of the American Medical Association. It took me many months to find these figures.

The percentage of patients in general hospitals under the age of thirty was 32.6 and over the age of thirty, 67.3. These figures were obtained by interpolation. It was necessary in the age group of fifteen to forty-four years to do a little free-wheeling since there was not sufficient time to get specific age groups from Dr. Dickinson.

In regard to the matter of hospital admission X-ray programs, as shown by the Public Health Service, let us consider the number of new cases which have been found per thousand X-rays: Among schools it is 0.25; among industrial institutions it is 0.5; among community surveys it is 0.7; and in hospital admission X-ray programs it is 2.2. Correctional institutions, homes for the aged, migrant labor, displaced persons, and slum areas are also other areas productive for X-ray screening.

Dr. Hofstra, who is Acting Chief of the United States Public Health Service Tuberculosis Program, wrote me a few days ago that there are nearly 22 million admissions to general hospitals in this country during the year. He could estimate that about 19 million or more of the patients were fifteen years of age or older. If we then apply his rate of yield, 2.2 per thousand X-rays, we get an estimated 43,500 previously unknown active cases by this technique.

Dr. Hofstra feels that these high yields from hospital surveys require much more publicity than is given at the present time. I think it does become reasonably clear that the chest X-ray continues to be a very important diagnostic tool in case finding and, as physicians, we ought to be quite sure that we do not let ourselves be diverted from this conviction.

I would like to say a little something very briefly about the effects of ionizing radiation as it affects our X-ray programs and our tuberculin testing programs. Many programs have been jeopardized, or all but jeopardized, because of the current attitudes on the effects of ionizing radiation. I cannot go into all of the reasons for this, but this subject of ionizing radiation certainly has become a source of extraordinarily conflicting emotions. Chest roentgenography has fallen prey to a variety of hysterias, and I think we might as well accept the fact that the ill effects of X-ray radiation are aimed at our gonads, certainly with disquieting fears of the unknown.

The unknown is really probably the most serious aspect of this. The effect on this biologic basis of life upon our future generations is something about which we are not by any means clear. I think it is of interest, however, that our radiologists, geneticists, and biophysicists really have no agreement in regard to these effects. I also think it is apparent that, since the fruit fly and the mouse have been the only sources of information concerning hereditary effects of ionizing radiation, there is, perhaps, room for some doubt about its application to human beings.

Fortunately, however, the gonads are quite a distance away from the chest in most people and, therefore, subject to maximal shielding from modern protective devices. Furthermore, the chest X-ray gives the smallest amount of radiation exposure to the body as well as to the gonads if properly taken and if carefully directed to the chest. Therefore, the emphasis concerning these effects of radiation probably is salutary. I think it has focused our attention on a problem that deserves it. Our radiologists, our physicians, and the public are entitled to the information that we get, and certainly we should emphasize that efforts be directed toward the modernization and frequent monitoring of our machines rather than upon the fear of radiation itself. Full utilization of roentgenography is terribly important for every program, and unless this can be done we are really at fault.

Actually, pressure from the medical profession

in regard to the need for X-ray has already produced extraordinary changes in the character of our machines and in the safety devices of all sorts, and I think that we can, without question, look forward to a wider utilization rather than a smaller one.

In closing, I would like to mention that an evening or so before I came down here, Dr. Shields Warren, who is the former Atomic Energy Commission Chairman, spoke to a small group of medical men on the effects of radiation in man. He discussed many angles of this which I will not go into except to speak briefly about the fact that he considered that atomic radiation had really become an absolutely essential peaceful instrument in modern civilization. He said it is the only source of heat and energy great enough to maintain our expanding world populations of the future.

He pointed out three ways that this can be regarded: first, a laissez-faire disregard of the effects of atomic radiations and atomic ash through, largely, fear of what will happen; second, a resort to atomic war; and, third, to work out an effective harnessing of its usefulness to man. He chose the latter method.

So, in case finding, tuberculin testing and roentgenography are the diagnostic weapons of choice and necessity. Radiation effects need respect, but can be made safe to be used as we wish to use them for man's benefit. Fear only of its effects is prejudicial to progress.

It would appear, then, that radiation of all sorts and roentgenography are here to stay; and the sooner we learn to live with them and to use them properly, the better we and all our case-finding programs will prosper.

DR. BOUCOT: Thank you, Dr. Badger. That certainly begins this panel at a very high level. I think you rightly emphasized that the major case-finding problem lies in our larger cities, so it seems appropriate next to call on Dr. Chapman, who has the responsibility for directing case finding for Detroit, a city about as large as Philadelphia. Let us hear what his ideas are on a suitable case-finding program for tuberculosis in a major city.

DR. CHAPMAN: Dr. Boucot, the problem of case finding for tuberculosis in a large city, I believe, is somewhat more complicated than it is in some other areas. I agree with what Dr. Badger has said, that we have been somewhat embarrassed by developments in the recent past; although these have not been fatal, they have been a little disconcerting.

The attitude which we have had for a long time has been that tuberculosis would be found in certain areas of the city more frequently than in others, and we have tried to center our attention on these areas whenever we were doing a community type of survey. Because of the size of the city and the number of available units, such surveys have been fractional. We never have had an opportunity to have a city-wide survey of the type that was once sponsored by the Public Health Service.

More recently we have been able to use additional facilities borrowed or incorporated from the state of Michigan, as well as some that we got on loan from the Public Health Service. For the last three years, in the most densely populated part of the state, we have had a corporation set up to help find tuberculosis, and we have called this the Southeast Michigan Tuberculosis Detection Project. We contribute our personnel and thoughts to this as well as some of our money, and we believe that this has helped keep us moving along in the direction of finding cases.

As to the lower limits of how far you should go with surveys of the X-ray type, we have felt that the yield that we have been getting thus far has been within permissible limits. In fact, about a quarter of our cases are found by survey efforts directly; that is, of newly reported cases. The rate per ten thousand is at the 10 per ten thousand level, and this is without really concentrating all of our efforts all of the time in the highest incidence areas.

We think that there are many hidden cases of tuberculosis in the community even today and that we will discover them by this method, particularly those persons who are ordinarily not seeking medical help until much too late and those who, for economic or cultural reasons, are not apt to see their physicians as often as they should.

We think this program must continue. We would like to have better devices to use, such as improved X-ray equipment, but, knowing the areas of highest incidence, we want to continue to concentrate on them. This is easier said than done because, among other things, these people are not always the most amenable to surveys. They may be ignorant about what we are trying

to do. They require somewhat different methods of approach to get them to cooperate. Among their groups there may not be too many so-called resource people who can help us get across the program of case finding.

From time to time we have borrowed students from colleges in the neighborhood to encourage cooperation. This has produced a good many examinations that we thought we couldn't get otherwise. We have stooped to such negative approaches as putting in a soup line and telling all those present that they couldn't get any soup unless they got X-rays. This works very well. I advise you to try it sometimes.

DR. BOUCOT: We have tried it in Philadelphia.

DR. CHAPMAN: Does it work?

DR. BOUCOT: It certainly does.

DR. CHAPMAN: I think that we should concentrate on other groups that you recognize, such as individuals who are in difficulty with the law; not the felons, but the ordinary misdemeanants and workhouse populations, and that sort of thing. We think there is lots of "gold" there, and we think we still should look for it.

DR. BOUCOT: Thanks a lot. I hope you have no regret at your inability to do one of those fast tempo all-out mass chest X-ray surveys. Do you, Dr. Chapman?

DR. CHAPMAN: At the time we would not have had enough beds to take care of the problem, and maybe we're just as well off. I think, though, that this kind of program must come back, maybe not on quite as large a scale, but it is our experience with a regional sort of thing that you can get enthusiasm worked up, and you can get people marshaled, and extra units, and things like that, and do a better job. I think this could be tried elsewhere.

DR. BOUCOT: As you know, the Public Health Service gave up this idea. When I went out to Pittsburgh to look into a solitary nodule study that the National Cancer Institute has there, I noticed that a great many women turned out for their all-out survey. While women have plenty of time, apparently it is among the older men that we obtain the highest yield.

What about contact work, Dr. Chapman? I am under the impression that the highest yield is from that good old-fashioned work on contacts of tuberculous patients.

DR. CHAPMAN: This is certainly true. Contacts yield excellent returns, but it seems that we have less facility to do this than we once had. We are constantly in competition with ourselves on many other programs; and tuberculosis has a difficult time, I think, getting as much attention as it once did. I say this, not in regard to the local level, but I think it occurs all over. The old-fashioned contact work that the classic public health nurse used to do is harder to get done, it seems to me. I don't mean that it shouldn't be done; it is being done, but there are large areas where it is not being done as well as it should be.

DR. BOUCOT: I think this is terribly important because we are launching on tremendous tuberculin-testing surveys all over the country. The minute radiation hazards came up it seemed as though, all over, there was a tremendous swing to tuberculin-testing surveys. I was very pleased to hear what Dr. Badger said about the low yield in Boston. Way back in 1945, the Advisory Committee to the Pennsylvania Tuberculosis and Health Association (the Medical Advisory Committee) suggested abandoning the tuberculin-testing programs in the state of Pennsylvania because of their low yields. Now, no case-finding program is any better than its follow-up. You would go along with that, wouldn't you?

DR. CHAPMAN: Yes.

DR. BOUCOT: So, if we can't follow our known cases, contacts to known cases, what are we doing launching tremendous tuberculin-testing programs? If we can't follow the known cases, we surely won't be able to follow the reactors we find.

DR. FURCOLOW: Dr. Boucot, is it because we are diffusing our efforts too much in the follow-up of contacts? Are the health departments continuing the follow-up of contacts beyond some point of maximal yield which should certainly be one year?

DR. BOUCOT: Let us ask Dr. Julia Jones to answer that one. She has a lot of information on follow-up of contacts, even of patients at home on home therapy.

DR. JONES: As you stated, my experience is limited to this group. I don't feel competent to speak for the health department activities, which are much broader. Because we have been interested in this question of patients treated at home with drug therapy, we have made an effort for the past almost-five years now to keep in touch with those living in contact with these patients. While we frequently do pick up previously unknown

cases when we first survey these people, we have not been finding any appreciable amount of tuberculosis developing as time goes on.

These are rough figures because they haven't been brought entirely up to date, but we have information on some 1,400 individuals living in the home, or members of the family of patients under treatment, this being 300-odd patients. Out of this group there have been seven new cases of new tuberculosis in this period. I don't really think it is seven because I would like to discard four who were tuberculin positive when the source case went home; but they, at least, have developed disease over a period of time extending up to four years. Had we stopped following them at one year, we would have missed them. It isn't very many cases.

The other three (and I think this is very important) were all infants, and the source cases were all people who left the hospital against advice, did not bring the children in in spite of great effort to get them, and did nothing they were advised to do. I think the answer here is the old problem of uncooperative people, so I feel fairly confident that, while it is important to follow these contacts as case-finding measures, it hasn't been very profitable in our hands.

DR. BOUCOT: Thank you very much.

What do you think about the follow-up of contacts, Dr. Chapman? Do you feel one year is an adequate length for follow-up of contacts to known cases?

DR. CHAPMAN: For practical purposes I think this is about as much as you can do in this field. The problem is too complex—the availability of help, and so on.

DR. BOUCOT: I am beginning to feel a little better about our Philadelphia program. We follow our contacts for five years here, and we had the impression we hit pay dirt. Unfortunately, I didn't know we were going to get into this area, so I don't have any data available.

Dr. Jones, would you like to discuss case-finding—the tuberculosis control program—in a hospital, Bellevue Hospital? Dr. Badger was saying that this gave such a high yield, 2.2 per thousand.

DR. JONES: The reasons that have been given for admission survey of patients entering general hospitals are familiar to most people, this being based on the fact that various surveys have shown a rather high yield from this group. It seems to me it should be suggested that this will vary, depending upon the community, just as Dr. Chapman indicated; that, within one community, there will be areas of high incidence of tuberculosis and other very low areas, and this is certainly true in New York.

I would think that what you would anticipate in a hospital survey would reflect tuberculosis in the group being served by that hospital and, as those of you who are familiar with the situation would suspect, Bellevue Hospital serves a high prevalence area, so the return has been relatively high. I would like to generalize a little bit more, though. There is another reason for making these surveys. I am discouraged—and I think most of you are who are treating tuberculosis—by the number of patients seen for the first time with far advanced disease. Without elaborating upon it, it has been pointed out in every panel we have listened to in the last two days that people with advanced cavitary disease are harder to treat than people who are found earlier. It perplexes me why, with all these case-finding activities going on every place, there is still so much previously undiagnosed advanced disease coming into the hospital.

We have been interested in the patients who die of tuberculosis with the idea that these were the recalcitrant people who interrupt therapy. To our surprise, when we really tracked it down, this isn't really the case. These people who are coming into our hospital and dying of tuberculosis are people who have never been previously diagnosed and, for some perverse reason of personality, stay in a lodging house some place until somebody has to carry them into the hospital. Then, when this happens, we are faced with problems about whether to give them steroids, and what combinations of drugs to try, and so on. I can't help thinking every time we see one of these patients that it would be so nice if we had seen them when their lesions were minimal.

The reason for mentioning this here is that, fortunately or unfortunately, these same people manage to have a variety of diseases, so they come into general hospitals and there, whether they are seeking to have their tuberculosis diagnosed or not, they are somewhat of a captive group and you can X-ray them. I think this is a very important point. These are people who are hard to reach and, if we can reach them because they

happen to have delirium tremens or fractured hips, then it is very useful.

DR. BADGER: Dr. Jones, may I interrupt to ask you a question? In our Boston survey we have an extraordinarily low yield on tracing back the tuberculin reactors. Only two individuals were found in our high incidence area. At the same time, from the same area, 70 per cent of our cases were reported from general hospitals. It seems to me that, somewhere or other, we are either losing these people by volition on their own part because they are escaping the searcher after tuberculosis—what you say is true. Do you think this accounts for our high yield on hospital admissions and our low yield on case tracking?

DR. JONES: I think it probably does. The group I am talking about is a group of people we all know who certainly would never step up to a mobile unit and ask to be X-rayed, but when you have them on a stretcher it is easier.

DR. CHAPMAN: Were those people children that you tuberculin-tested in Boston?

DR. BADGER: Children in the grammar-school age.

DR. CHAPMAN: In other words, the people that came into the hospital quite ill didn't have children.

DR. BOUCOT: They are mostly lone old men who live in the tenderloin districts, aren't they?

DR. BADGER: Not entirely, no; but actually nearly 30 per cent of them were from the age groups of thirty to fifty. They are a fairly large group, so they are not just old men, I can assure you from my experiences both at Bellevue and Boston City, which are quite identical.

DR. BOUCOT: Dr. Jones, as long as you have been interrupted, let me ask you this question: What are you doing at Bellevue about prenatal patients? The other day at Woman's Medical College Hospital, a woman arrived in the emergency ward in active labor; she delivered in the emergency room, was then taken upstairs, and was noted to have a high fever. She turned out to have bilateral advanced tuberculosis. Her sputum was loaded with tubercle bacilli. She had never been near any hospital during her prenatal period. But what is your plan for prenatal patients who do attend prenatal clinics?

DR. JONES: In thinking this over, I hoped that I could pin some of the rest of you down on this thing, because I know, in thinking about surveys, it has been advocated that pregnant women have tuberculin tests before they have X-rays. The reasons for this are fair enough and yet I can't erase from my mind the mental image of the Bellevue prenatal clinic swarming with people speaking all languages, and each accompanied by four or five small children who have come along because there is no one to look after them elsewhere.

It is a fair job just to get them all seen without having somebody do tuberculin tests on them; and then to get them back for reading rather defeats me. All of this being true, I wonder if it isn't better to take the X-ray, if you can get around to taking one X-ray in a fairly reasonable way, rather than to take a chance on what you just reported. If you get into that mess, then you have four babies at home and the mother in the hospital with the new one, and all kinds of problems.

DR. BOUCOT: I am delighted to find that is your point of view. Again at Woman's Medical Hospital, as soon as the radiation hazard problem was raised, we asked the Obstetrical Department if we could immediately stop taking routine miniature films and shift to tuberculin testing. The obstetrical staff said, "Oh, no, you can't do that; you have found dermoid cysts, a carcinoma, and too many other nontuberculous diseases."

So we said, "All right, we'll do both and see what we would miss if we only X-rayed the reactors." To our amazement, in a hospital in a much better socio-economic area than Bellevue, we found that 50 per cent of the women tuberculin tested did not return for their readings without tremendous special effort, mostly for very valid reasons, such as children at home, the carfare, and so on. We would not have had the results on 50 per cent if we had relied on tuberculin testing alone.

What are you doing, Dr. Chapman?

DR. CHAPMAN: We are X-raying these women prior to delivery or at the time of delivery, if we miss on that. I think, however, that the recollection of several cases of meningitis that have occurred subsequent to delivery of a mother who was involved in active tuberculosis but who had not been examined have influenced us a little bit here in not dropping the X-ray since we can't get tuberculin testing done.

DR. BADGER: I just want to say one brief word about this business of the X-ray and what kind should be taken. It is still extraordinarily difficult

to answer that question, and there is so much and such wide difference of opinion.

We have a situation also in Boston which is unique in that, at Massachusetts General, they have discarded all of their 70-millimeter machines as too dangerous. On the other hand, at the Harvard Medical Center, with the Peter Bent Brigham Hospital and all the hospitals around it, the 70-millimeter machines have been fixed up with the most modern contrivances of all sorts and they take X-rays on all comers, feeling that the danger is little or none. They have hazards so reduced in roentgens and milliroentgens that it is considered quite safe. So I think you can "pay your nickel and take your choice" on this, but the most important thing is that the machine should be adequately taken care of.

DR. BOUCOT: Dr. Hart, do you have any idea what the practice is in England or Africa? You mentioned that your primary interest is not case finding and we are not ignoring you, but we are trying to ask only questions to which the answers may be familiar to you.

DR. D'ARCY HART: I know something about mass radiography practice in England.

DR. BOUCOT: Do they encourage prenatal patients to report to their mass radiographic units?

DR. D'ARCY HART: Yes, or they are done in the antenatal clinic in the hospital, but the question of danger of X-rays, and so on, is still very much unresolved.

DR. BOUCOT: Is there much anxiety about it in England?

DR. D'ARCY HART: Yes. Actually, it may sound laughable, but quite a lot of people are taking refuge in the fact that a very big report is supposed to come out, which gets delayed month after month, of a committee which is going to tell us the dangers, and we have had to depend quite a lot on leaks before this. I think we are moving in much the same direction as in this country. There is a tendency at the present to prefer large films and to think they are safer, but we are aware that the lead is being taken here to reduce the risks of the miniature machines. But that has not been advanced so far in our country and, at the moment, I think it is generally considered that a large film is safer than a small film.

DR. BOUCOT: Dr. Canetti, do you know anything about the situation in France? I was interested, in Stockholm in August, to hear a paper by Etienne Bernard and his colleagues in which they mentioned following patients, clinically ill patients, by serial photofluorograms. Is that a common practice in France?

DR. CANETTI: As far as I know, it is not a common practice. I am afraid I can't give you elaborate information on that.

DR. BOUCOT: Dr. Holm, do you want to make any comment about miniature versus conventional 14- by 17-inch films around the world?

DR. HOLM: This problem was discussed at length in a conference in Stockholm in September, and I think it was the general consensus that the risk was very much exaggerated. This hysteria about X-rays exists only in a few countries, mainly in this country and in England. In Europe it is much less. In Germany, for instance, where they have made exact measuring of the X-ray on the gonads, they have come to the conclusion that, if a person should come to the permissible limit of dosage, he could have an X-ray every day in the first thirty years of his life. Therefore, from such considerations, they didn't think there was any real risk if the apparatus was correct. It is a very important point.

DR. BOUCOT: Dr. Jones, have you finished what you were going to say about the hospital case-finding program?

DR. JONES: No, not quite, because I don't want to give the impression that I think all you have to do is set up a roentgenographic machine and have a survey, which is easily arrived at, tell the X-ray man to X-ray, and then everything is all right. This is certainly far from the case. I think some emphasis should be made on the fact that there is more to it than taking an X-ray film. We have mentioned the use of the tuberculin test as part of this program for certain special groups, such as children, young adults, and pregnant people. It is so important that it be kept firmly in mind that one reason for doing this is to get these people under treatment; a second reason is to protect the hospital personnel from tuberculosis. Unless there is very careful follow-up after the film has been interpreted, this isn't going to be achieved just because someone read the X-ray.

Where it is a "big operation" this is a real consideration because I think many general hospitals are not staffed to take on the extra tasks of the survey, and are not even well enough informed how to do it or are in sympathy with it. I find

some of the general hospital people I deal with are "playing ostrich" about tuberculosis. They don't believe in it. All they care about is that, if they have a case, somebody take it away fast and, until someone takes it away, they put a basin outside the door and wear a mask and this is the limit of their understanding of the problem.

I don't think you can expect good results from a survey in that environment. In the first place, a patient who is shoved behind an X-ray machine without any explanation is apt not to come back when you need him, so I think all of this needs quite a bit of thought.

Finally, of the people who have been turned up in our admissions survey, there have been a certain number with obviously active tuberculosis; but, predominantly, a lot of the patients have been in the category mentioned in yesterday afternoon's panel, people with disease of unknown activity. The question of what to do with them, I think, is a very real one.

I mention this because I think we have inherited an attitude of "well, that's just an old scar in your chest; forget about it." You will recall that, in the discussion yesterday, no one could agree whether they should be treated or not, and I certainly would go along with the fact that, if they are followed closely, that probably will take care of it. Unless everybody takes seriously these lesions that are picked up in these surveys, I don't see any profit in having the surveys.

A number of us have been commenting about this and have mentioned the fact that, quite frequently, a patient is admitted with advanced active tuberculosis. Then, you reach in the folder and pull out a film made a couple of years ago which shows one of these lesions to be of questionable activity. The film might as well never have been taken as far as I can see. This thought about the lesion which is not obviously active is an important part of getting profit from the survey.

DR. CHAPMAN: I would like to comment on the point that you raised, Dr. Jones, about the inactive case diagnosed as inactive the first time. Several years ago we had reason to review a large number of minimal inactive cases so diagnosed by a very experienced radiologist who was with us at that time. It appeared that, within a two-year period following the diagnosis, 12 per cent of these individuals who had been examined showed active tuberculosis.

I think that this is a conservative figure and, since the number of cases that are adjudged inactive in our experience is about three inactive to one active, I think this represents a problem which is hard to follow, but it is nevertheless very real. I think that we find, just as you have, old X-rays stuffed away somewhere which means that we have missed something.

DR. BOUCOT: I think the single most valuable thing you can do when there is any chest abnormality is to try to find earlier films. No single film is very definite in regard to activity. Would you go along with that, Dr. Badger?

DR. BADGER: Yes, absolutely; that is most important.

DR. BOUCOT: George Sommer has been doing tuberculosis case finding in mental institutions in New Jersey. What has been your experience there?

DR. SOMMER: I thought I would first mention this question of the examination of the new patients. Only in the last year have we been doing tuberculin testing at the New Jersey State Hospital in Trenton, and I have some data on results. In the course of a year we examined 1,258 new patients with an intermediate dose of PPD. Of these, 674 were white males with 360 positive reactions (53 per cent). One hundred and thirty-eight were nonwhite males, with 62 per cent positive reactions. The white male positive reactors had an average age of forty-six years. The nonwhite positive reactors had an average age of thirty-five years. The negative reactors were slightly younger. The whites averaged thirty-one years and the nonwhites twenty-nine years.

There were 368 white females examined. Of these 38 per cent were positive reactors. There were 78 nonwhite females; of these 60 per cent were positive reactors.

The average ages were forty-six years for the white females, and forty-three years for the nonwhites. This is for the positive reactors. Negative reactors were slightly less, both approximately forty years.

It is worth while to compare these data with a school population in our own county, Mercer County. The State Hospital at Trenton takes care of several counties, the chief city being Trenton. In Mercer County (about half of which is suburban and rural and half the city of Trenton), there was an average in positive skin sensitivity of 6 per cent in some 21,000 school children examined.

DR. BOUCOT: What grade was that, Dr. Sommer?

DR. SOMMER: From kindergarten to twelfth grade, alternating grades; they did half the grades. The skin sensitivity was 1.5 per cent in the kindergartens and had risen to 6 per cent in the twelfth grade. It might be noted that the incidence of positive reactions was somewhat lower in the parochial schools, which have a lower nonwhite population than the public schools.

DR. BOUCOT: Dr. Sommer, could you go back to the records of the mental institution and tell us how much active tuberculosis you found there?

DR. SOMMER: Yes, I have the data here for three years. During that time the average population of the institution ran about 3,600 a year, with admissions from 1,300 to 1,450 a year.

Our detection program is as follows: We examine each patient on admission by a photofluorogram with, of course, a check-up on larger films and then clinical and bacteriologic evaluations on the suspected cases. We have a semiannual photofluorographic examination of all patients and employees. This may seem a quite frequent examination, but in my experience it is necessary among the mentally ill. A large number of patients come to us from other mental hospitals and from other tuberculosis hospitals.

I will refer to the patients picked up on routine examination. In the three years, with approximately 4,000 admissions, we found 21 new cases by routine examination. That is approximately 5 to a thousand, which is over two and a half times as many as are found in the general hospitals.

In our surveys in these past three years we found eight cases that we regarded as reactivated and we have fourteen apparently new cases found in these three years. That is from approximately 22,000 examinations.

It is my impression that these so-called new cases are really reactivations in older people in whom insignificant lesions were not considered to be present in earlier examinations, rather than cross-infections in the hospital. I say that because we have had a small experience of checking back on our tuberculin-negative patients who were admitted to the hospital and then discharged in the past year. Of those tuberculin negative, we have examined 377 (those dicharged within the year after three months in the hospital), and none of those patients in the hospital less than a year after their negative reaction on admission examination had a conversion from negative to positive tuberculin reaction. Of those in the hospital for a year we only had a small number, 33 cases. One of those patients converted from negative to positive. I think those figures on the single conversion would indicate that we are not having cross-infection in our hospital population.

DR. BOUCOT: Thank you very much. I think that sounds like an excellent tuberculosis control program.

DR. SOMMER: There is one other thing I must mention. Of course, our known and strongly suspected tuberculous patients are isolated and followed in an entirely separate program, so that the photofluorographic surveys made twice a year do not cover the known tuberculous patients.

DR. BOUCOT: Just before we leave mass chest X-ray surveys and hospital surveys, I would like to poll those concerned on the panel as to whether or not they feel that 14- by 17-inch films should be substituted for photofluorograms wherever feasible. I think Dr. Hart mentioned this.

DR. D'ARCY HART: I only said that the people would prefer that in very small groups. It is quite impractical for mass roentgenography in general.

DR. BOUCOT: Do you really prefer 14- by 17-inch film in any group for case-finding purposes?

DR. D'ARCY HART: I can only say that I am personally concerned only with the protection of laboratory personnel, and after asking advice all around, including Dr. Bignall's hospital, we came to the conclusion that, with such small numbers, we should give them the benefit of the large film. I think that is purely a temporary expedient until the miniature machines are made safer all around, which is not so at the present time in England.

DR. BOUCOT: How about you, Dr. Jones? Do you feel that you would prefer for case-finding, if you had to take one single film, a 14- by 17-inch to a miniature film?

DR. JONES: As I see this, it is a matter of expediency.

DR. BOUCOT: I am asking a different question. If you had your choice and there were no other considerations, and you could take one film on a person, would you feel that a single 14- by 17-inch film was preferable for case finding to a single miniature film?

DR. JONES: Yes, I guess so, partly because (if I can throw in this qualification) you are required to take a second film on a good many people with the miniature film. I don't feel very strongly about it except for these special groups. It doesn't seem to me there is any point in taking children or pregnant women on the photo-roentgen.

DR. BOUCOT: How about you, Dr. Chapman?

DR. CHAPMAN: It seems to me you are asking whether or not I prefer a Cadillac to an Isetta. As far as I know, I prefer a Cadillac. I never had one, but I think I would. Other than that, you know the old reviews of the efficiency of finding something wrong—that the small films were pretty effective this way, and that is the end of the scale I am usually thinking about.

DR. BOUCOT: I think the miniature film is the Cadillac. That is the only difference in the opinion we have. I feel that, for case-finding purposes, the miniature film condenses and exaggerates, and is superior to a single 14- by 17-inch film. How do you feel, Dr. Badger?

DR. BADGER: I think as a diagnostic film the 14- by 17-inch is superior to the other, and most of the errors that have occurred in our own experience with the chest X-ray screening programs with the miniature have been that (we haven't had as good luck as you have had in Philadelphia) lesions have been overlooked by competent observers and the patients have proceeded to go into advanced disease before they got through. I prefer the 14- by 17-inch, but, if I can't have it, I'll take the other.

DR. BOUCOT: Now we had better shift to—

DR. D'ARCY HART: Are you leaving this subject? I would like to make another point. There seem to be two points which I don't think have been considered, unless I wasn't noticing. One is the question of how far the available energies of mass X-ray work should be spent on examining the same lots of people more than once, repeatedly; or whether to use that effort for having more people done once. That is a matter of controversy, at least in Britain, and I should be surprised if it wasn't here.

The second thing is the whole question of to what extent people are volunteering and whether it matters that a significant percentage don't turn up; how to increase that, and so on. That seems to be extremely important, "What makes people come?" It is a voluntary process here nearly always just as it is in Britain.

DR. BOUCOT: Nearly always. In this particular city our foodhandlers are required by law to report once a year for check-up. We find a much higher yield in volunteers than in the foodhandlers.

Does anyone else want to speak to this point?

DR. BADGER: One other word, and that is that we found in the mass Boston survey that the important people we wished to find did not appear for X-ray. One of the reasons why I have long supported the hospital admission X-ray program is because, as Dr. Jones has already said, you can find a lot of people with tuberculosis who come in for other reasons.

Also, our tremendous reservoir of new and old cases are, many of them, hard to take care of. Many of the patients know they have tuberculosis. They will certainly not report if they are disinclined to do so. Recalcitrant patients, above all, will be found and perhaps be kept better track of by a hospital admission program than by voluntary efforts on the part of a good many people to get them.

DR. BOUCOT: Do you have any strong convictions, Dr. Chapman, as to whether it is preferable to re-examine high-prevalence groups than to try to do a larger segment of the population once?

DR. CHAPMAN: I think it would be more valuable to go after the areas of high prevalence. I still think tuberculosis is an infectious disease, and where we know it is, is where we're going to find it. If we look at the survey of captive groups, like foodhandlers, we get about less than half of what we get when we look at the areas of higher prevalence, quite a bit less than half.

DR. BOUCOT: In Philadelphia, the unit where the foodhandlers report has a yield of 2 per thousand previously unknown proved active cases of tuberculosis and, in a unit up in the area of high morbidity and mortality, the yield is 8 per thousand.

Now, to sum up what we said about mass chest X-rays (and we haven't had time to go into many of the details): I gather that it is the opinion of the panelists engaged in this work that they should not be abandoned; that they should be beamed toward high prevalence areas, particularly to hospital populations and those areas of large cities with a high mortality and morbidity rate.

There is a difference of opinion as to whether 14- by 17-inch or miniature films would be prefer-

able. Certainly 14- by 17-inch films are not practical for large numbers of people.

So far as periodic X-ray versus single chest surveys, Dr. Chapman feels that he would settle for one X-ray and I don't know that we really have data to argue the point.

DR. BADGER: I think perhaps we are laying too much stress upon the 14- by 17-inch and its probable cost. Actually, as figured out by various groups, a 14- by 17-inch film costs about a dollar if any number of X-ray films are taken. It may be more in some localities where fewer films are taken. But if the decision is that a 14- by 17-inch is a better film and that is what you want, then certainly it is just as valuable to a patient not only with tuberculosis but with nontuberculous disease in picking up things that are really important. We do a lot of other laboratory work on our patients for which they pay more than a dollar—more than a dollar and a half—and I sometimes wonder how much of that is really valuable and whether money isn't being wasted in areas where it has no business to be spent, and whether we can't more wisely use it on the X-ray.

DR. BOUCOT: Thank you, Dr. Badger, but I have to say the last word as moderator. I strongly protest any trend toward substituting 14- by 17- inch films for miniature films because it has been such a frequent experience of ours that a lesion has been picked up, particularly lung cancer, on the miniature film; and the 14- by 17-inch retakes, taken by clinicians, were read as negative while the subsequent course of the disease proved that the miniature film was right because it exaggerated or penetrated the heart or the bony structures because of its technically different features.

In Philadelphia we don't do routine 14- by 17-inch retakes. We feel, if there is any suspicion on the miniature film, the subject should be rushed to the clinician for careful investigation and not a single film.

I want to say one more thing about cost. The cost of any roentgenographic screening examination is much more than the cost of the film. Dr. Jones mentioned the need for follow-up. One must include in case finding not the cost of the film alone, but the cost of adequate record-keeping and careful follow-up.

Now, Dr. Badger, you may have the last word.

DR. BADGER: I just wanted to say that I think there should be more careful study of the differential errors that occur in these two fields. We all remember the given case that turned out to be wrong by 70-millimeter and turned out to be wrong by the other. This may be an individual difference, but I still think, in the long run, that your 14- by 17-inch is really a superior diagnostic film.

DR. BOUCOT: Good. We have Dr. Feldmann on the panel, and we will make an application for a grant to the American Trudeau for a careful statistically significant study on the subject.

Now we would like to turn to you, Dr. Feldmann, for something else. Talk to us for a moment about tuberculin case-finding programs. These are being extensively launched upon by many tuberculosis associations all over the country, aren't they?

DR. FELDMANN: I am afraid we are in a period when tuberculin testing is a very popular affair, and I would like to say right now that we have not promoted this particularly and I think this enthusiasm has resulted on several sides from causes of several kinds.

In the first place, the radiation fears have had something to do with it; but I think, before that, the real reason that many of our case finders have become interested in tuberculin testing is that the yields from some of these large-scale hit-or-miss X-ray surveys has fallen so low that they were uneconomic. No one, so far as I know, has ever set a point at which you can say a particular procedure is economic or noneconomic. It is something like trying to put a value on a human life; nobody has ever been able to do that exactly. I believe that most people have drifted toward the opinion that, if you get less than one new active case per thousand X-rays taken, perhaps you had better look into the procedure to see if you couldn't better it.

These have been reasons I think, for greater interest in tuberculin testing and I think, too, that our approach to the use of the tuberculin test is a little bit different in these latter years than it was in the earlier years. I think we have had a better appreciation of some of the difficulties involved in tuberculin testing and, at least on the part of the National Tuberculosis Association office, I think we have tried to keep our people informed of some of these difficulties.

We have been handicapped by lack of data. I think we have tried to impress the people who wanted to do tuberculin testing that, if they were going to go into some kind of program, this was

not an easy thing that would solve all problems in case finding, but that it was an opportunity for them to find out something about its potentials if it had any.

DR. BOUCOT: Do you recommend case finding as the goal of tuberculin-testing programs?

DR. FELDMANN: I think that is part of it, Dr. Boucot. There is a very high risk rate if there is an infection in infancy. That we know. We also know that, when a positive reaction is found in children in the younger school ages, very few of those are going to progress immediately to active disease; and we know there is a rising risk rate during the teen ages.

The thing that bothered me about the discussion the other day on the use of prophylactic treatment was that we seem to stop at age twenty, and it seems to me that the usefulness of the tuberculin test doesn't stop at age twenty; but that the peak of the risk rate, as nearly as we can tell, is somewhere between ages twenty and thirty. So I would think, if you were going to use isoniazid prophylactically, that you would have even more reason for using it in people with positive tuberculin test reactions in this age group from twenty to thirty than you have at age fourteen.

Another thing that we did the other day was to limit this pretty much to females in the younger age group. If you draw a curve for males and females, however, you will find that, although the female rate is higher, it is not very much higher, and that the lines seem to cross shortly after the age of twenty. They run along pretty much together at these two places.

This, I think, gives us a sort of baseline for case finding. If we have some of these data on a population group, we can start then with this as the people at greater risk. Then we can go on to these other people who have still higher risks in these different groups. I have heard the term "traps" used for these people in the population whom you might get in for examination. I don't know whether you want me to go any further on this or not.

DR. BOUCOT: You mentioned the ones at greater risk, and, in Panel One, there seemed certainly to be unanimity on the advisability of treating with isoniazid infants under age three.

Dr. Lincoln, will you please tell us what you think we should do to find reactors in babies under age three?

DR. LINCOLN: I think the most important thing is to make use of a tuberculin test and a form of tuberculin test which can be administered frequently.

DR. BOUCOT: How early would you start; the day after birth?

DR. LINCOLN: No, I think in routine tuberculin testing that pediatricians or others who see children should be encouraged to do tuberculin tests beginning, certainly, with the age of six months; and we have been trying to encourage people to begin with the age of three months as part of routine physical examination which the majority of small children now get.

DR. BOUCOT: That is a very important point. There has been some talk about infants younger than three months being unable to react to tuberculin. Is that true?

DR. LINCOLN: No. I think or I know that we have seen children as young as the age of six weeks with positive tuberculin reactions. We don't see as many, of course, but I think that probably reflects the low rate of infection in the very young. As far as I know, nobody ever tried to tuberculin test them unless there was a direct history of exposure in the first month of life. I don't know the youngest it has ever been, but we have seen them at six weeks.

DR. BOUCOT: Dr. Hart, you said something at that panel, if I recall correctly, about the importance of the size of the tuberculin reaction. Dr. McDermott mentioned larger than 10 millimeters. That didn't seem very large to me. Did it to you? Were you referring to reactions larger than 10 millimeters when you spoke of strong reactions?

DR. D'ARCY HART: I can only deal with a particular experience in a particular trial, and that happened to be a test to 3 tuberculin units. In dividing up the different diameters we found the most useful division was at 15 millimeters and, at 15 millimeters or over of induration, that strength of tuberculin did show a very marked difference in incidence of tuberculosis from the lower diameters 5 to 14.

We took our measure of any positivity at all at 5 millimeters, so 5 to 14 had a much lower incidence than 15 millimeters and over. But there is a certain artificiality and that was the way we did it in that particular trial.

DR. BOUCOT: Dr. Furcolow, you are the expert on our panel on tuberculin testing, the techniques, and so on. What is your feeling about size of reaction in relation to dose of PPD and subsequent clinical significance?

DR. FURCOLOW: I think it has been quite clearly demonstrated by studies all over the world, including the one that Dr. Hart mentioned, the Public Health Service study, studies in India, studies among U. S. Navy personnel, and others, that the size of the tuberculin reaction has a marked relationship to the development of tuberculosis in the individual. This has been found by follow-up of individuals. If you have a large reaction, more than 10 mm., you have a much greater chance of developing tuberculosis than if you have a small reaction. Actually this relationship, although not carefully calibrated, seems, roughly, to increase with the size of the reaction. I am speaking now only about reaction to a relatively low dose or the intermediate dose.

In our studies in Kansas City we demonstrated also that the yield of tuberculosis among the contacts of children in the kindergarten or first grade is related very closely to the size of the reaction in the index child. In other words, if a child had a reaction of 5 to 9 millimeters, the yield was something like 3 cases per thousand. This is a yield of new, previously unknown tuberculosis. However, if the reaction was 25 millimeters or over, the yield was almost thirty times as much as it was among the children with small reactions. There is no question, then, that the size of the reaction is of great importance in the yield of tuberculosis.

DR. BOUCOT: Suppose you were asked for advice by a community that was going to undertake a tuberculin testing program for its school children, and it had limited facilities for follow-up. Would you think the community would be wiser to use a weaker tuberculin and, therefore, screen out those who react to a small dose of tuberculin; or should this community use the intermediate strength and take only those who react, for instance, at over 25 millimeters?

DR. FURCOLOW: It would seem to me that we have a very good economic tool in the 5 TU by size. In other words, if you have facilities for a limited number of follow-ups, you take only those over 25 millimeters who are obviously going to be a relatively small number (this is millimeters of induration) and come down in follow-up by size of induration in accordance with your economics. This would make more sense to me than decreasing the strength of the tuberculin, in which case you would miss some of the people you are very anxious to get.

I want to say clearly that there has not been a correlation established, to my knowledge, between the size of the reaction and the presence of tuberculosis in the individual. This was tried a number of times as far back as 1938 by Dr. Long and others, and has been tried repeatedly since. I think there are some suggestions that may be true; but, actually, there is no clear evidence that the size of the reaction at the time of the test can be correlated with activity of disease, in other words.

DR. BOUCOT: Will you tell us something about the technique for these large-scale tuberculin testing programs? Should we use separate syringes, platinum needles, or a new needle for each case? Give us a little top-flight information about technique, will you?

DR. FURCOLOW: The virologists have been giving us a little trouble on whether we should use the platinum needle technique. Actually this was the main subject of discussion at the last committee meeting on tuberculin testing of the American Trudeau Society. At that time this committee unanimously passed a fairly strong resolution stating that there was no evidence of the transmission of hepatitis or other infectious disease by the use of either separate needles for each test or of the needle flame-sterilized between tests.

The reason this is of importance is that, if one is going to have to change needles between each test, this slows up the procedure considerably; but if one is going to have to get a new syringe between each test, this makes it almost impossible, because of the number of syringes which must be prepared, the wastage of tuberculin, and the delay. In addition, the solution is not as simple as it sounds in the procuring of plastic syringes, as in Cleveland, because it has been found that the silicon used to lubricate these plastic syringes absorbs tuberculin and, indeed, the plastic syringes themselves may well absorb tuberculin, so that this problem is not solved by the simple

means of getting a single plastic disposable syringe for each case.

However, the committee felt that no evidence had been demonstrated of the dangers of transmission of any of these diseases, and, until such evidence was forthcoming, that we could continue the recommendations as has been done in the past.

DR. BOUCOT: Dr. Canetti, what is the feeling in France about the use of separate syringes for administration of the tuberculin tests?

DR. CANETTI: I can't give you any information on that.

DR. BOUCOT: Dr. Holm, would you like to speak on that point?

DR. HOLM: In our program, of course, we make plenty of tuberculin tests. In our international campaign we make something like two million per month, and we use the technique of the same syringe flamed in between.

DR. BOUCOT: With a platinum needle, flamed in between?

DR. HOLM: Not necessarily a platinum needle, a steel needle even; and we have had no indication so far that we have caused any harm. I must say it would be difficult to ascertain; but we are using the same technique, for instance, in Denmark, where we have much better control over it and where we have no indication that the use of the same needle can transmit or will transmit the viral infection.

I would like to cite also that all over we are using one dose of tuberculin only, which corresponds to the 5 TU. We are going to change to the 1 TU, but that is for very specific reasons. We have found out that a good part of the tuberculin in the final dilutions is being absorbed in the glass. By adding a new diluent, we can avoid this absorption. Indirectly, this makes the tuberculin much stronger, so that, using a diluent, we get the same biologic reaction with the use of 1 TU as we used to get with 5 TU.

DR. BOUCOT: That is intensely interesting.

DR. HOLM: I should like to make one point more, that, in the use of the tuberculin test, the most important thing is to use a well-standardized tuberculin. For this reason, we prepared, in 1949, one big batch of tuberculin which has been used up to now in all of the programs. Now this batch is exhausted and we have prepared a new batch of tuberculin so big that there should be enough to cover the whole world's needs for the next ten years.

DR. BOUCOT: That is a fascinating report. We have two professors of preventive medicine in the audience. Dr. McDermott is near a microphone and maybe Dr. Herbert Edwards would step forward. Dr. McDermott, do you have any strong convictions about the use of one syringe and flaming the needle between tests?

DR. MCDERMOTT: I think it is the classic example of how we interfere with the environment and get into trouble. Dr. Holm put his finger right on the thing when he said "so far as could be ascertained," for, as I'm sure he would agree, that really means nothing. From 1910 until 1944, or so, antisyphilitic drugs were administered intravenously and there was no evidence during that entire period that there had been any transmission of viral hepatitis. It was all "arsenic jaundice" in those days.

Surely, the epidemiologists in our midst would tell us that the transmission of hepatitis by tuberculin testing could be going on on quite a scale and we simply would not know it. So that I think what we have to do is take a decision of practical wisdom, and perhaps that practical decision, like so many other practical decisions, should be taken on the score of the magnitude of the problem. By that I mean, in an area of high prevalence where the big problem is the tuberculosis and not a theoretic chance of transmitting viral hepatitis, then it seems acceptable to flame the needle and "boil your tools," so to speak. In areas of low prevalence I think we should not be quite so cavalier in tossing out this possibility of hepatitis. I think we simply have to constantly face up to the fact that, in tuberculin testing or anything involving syringes and needles, we may be spreading another disease which has its own case fatality rate, and that we should try to work out the practicalities of it.

DR. BOUCOT: Dr. Edwards, do you want to add anything to Dr. McDermott's comment?

DR. EDWARDS: I am afraid I can't add very much except to say that at Yale University we use individual needles for our nurses and medical students, and we have constantly. But the students are limited in numbers and, therefore, it is rather practicable. For the work we are doing

in schools now, we are using the platinum needle and flaming in between. That is based quite largely on the recommendations of the American Trudeau Society and, as long as the work is not too pressing and can be done with care, we feel we are quite safe, although we can't prove it.

DR. BOUCOT: Dr. Furcolow, will you go back to this point Dr. Edwards just brought up, "as long as the work is done carefully." Should teams be specially trained or do you feel tuberculin testing is a very simple procedure and that anyone can do it readily?

DR. FURCOLOW: It really seems to me that it depends on what you are trying to do with the tuberculin test. We have always felt that, if the tuberculin test were applied by the average physician in his office, we would be going a long way toward the control of tuberculosis. Obviously, this means, then, that we must have a test that is fairly easily interpreted.

On the other side of the picture is the fact that many physicians are actually not well trained in the reading or in the performance of the tuberculin test. If one is going to make something of the data in terms of surveys or reports, it is essential that as few people as possible are concerned with the testing and the reading of the reaction because it is obvious from what we said before that the reaction must be measured. If the tuberculin has not been given accurately and the reaction measured accurately, one has very little idea of what is going on. Therefore, a standardized dose of tuberculin, given as carefully as possible, with the reaction measured accurately and recorded, would seem to be the ideal. If we are doing surveys, as few people as possible should be concerned with giving and reading the tests, and the reactions should be measured as carefully as possible.

DR. FELDMANN: May I put something in here? After this discussion of all of our problems with the techniques of tuberculin testing, it seems to me this is a good place to bring up the point that we haven't improved our technique to speak of since 1908, and that it is about time we had a new gadget or new way of doing this test which would make it possible to give individual tests so that the gadget could then be disposed of. It would get us entirely away from this problem of homologous serum jaundice or sterilization and many of these other things. I think such a thing should be possible in this day and age; and yet we don't have it. Maybe this could lead to some of these other techniques that are in some use. Did you want to take those now?

DR. BOUCOT: The Heaf test is a new test, a new gadget, anyhow. Dr. Bignall, do you want to tell us about the Heaf test which is, I understand, used fairly widely in England. Is that true?

DR. BIGNALL: I think it is becoming much more widely used, particularly since a trial carried out by the British Tuberculosis Association, which compared the reaction given by the ordinary Mantoux intradermal tests with those given by the Heaf puncture test, showed that the two gave, in fact, remarkably comparable results. It is thought that the Heaf puncture test is approximately equivalent to the 10 tuberculin unit intradermal test. I believe, myself, that it is a very good test indeed, particularly for use in children. You never make them cry.

DR. BOUCOT: That is a very desirable goal, but Dr. Furcolow seems to have some reservations.

DR. FURCOLOW: I do with the tuberculin supplied with the Heaf test. In correspondence with Dr. Heaf, I am sure, although I could be mistaken, that he told me he thought the test was equivalent to about 100 TU, which is a little strong for our use. Moreover, looking at it from Dr. McDermott's point of view, the Heaf test is by no means the answer to the problem of viral hepatitis transmission. This, if anything, is worse.

If you use the tuberculin for a multiple test, for instance, the tuberculin adheres to the points. You can't use histoplasmin, for instance, with the Heaf apparatus because it adheres. This means separate Heaf machines for any kind of test you use. The question of sterilization, while relatively crudely answered, is far less clear, it seems to me, than at least when you get a flaming needle red hot and are fairly sure of something about the temperature. You dip the Heaf machine in alcohol and light it on fire and you hope it is sterile, and that's about it.

DR. BOUCOT: You cast some aspersions on the ability of individual inexperienced physicians to administer or to read the tuberculin test. We

have an internist here on the panel, and I would like to know what he thinks about case finding by the practicing physician and pediatrician. Do you feel we can trust these boys to do tuberculin testing?

DR. BADGER: That is a tough question to answer. I think it probably requires an educational program which goes way beyond what we are doing at the present time. I must say that my own experience with this has not been too exciting, and the necessity to re-do tuberculin tests which have been called negative, for example, has really been quite astonishing in the diversity of results that have been obtained.

I think pediatricians have an extraordinary opportunity for utilizing the test with better knowledge of the mechanism that they are using. I think they look upon it too often as a case-finding technique when actually, as a practicing physician, I find its usefulness greater in excluding tuberculosis than using it as a case-finding process. I think that this should be stressed very widely and I think in any tuberculosis program that we, as people interested in this disease, stress the case-finding mechanism too much; and actually, in practice it is more important in excluding tuberculosis than it is in actually finding it.

DR. FURCOLOW: The difficulty, Dr. Boucot, is not that physicians can't do tuberculin tests. They have never been trained to do them. After all, they have learned a lot of new techniques. For instance, how do you decide whether a patient is responding to cortisone. We never heard of that when we were in medical school. They were told how to do a tuberculin test, I guess, but nobody ever really made them do it and, second, they never had to measure it.

DR. BOUCOT: Do you think it is better for them to use patch tests because you think they don't know how to do intradermal tests?

DR. FURCOLOW: The patch tests are worse to read than the tuberculin tests, Dr. Boucot, and, even when carefully read, have a sizable positive and negative error. I haven't the faintest idea what an untrained person gets when he looks at them, because I have seen the most wonderful results and the worst results possible.

DR. CHAPMAN: I would like to ask you whether or not you have had any luck with pediatricians cooperating and using the intradermal tests rather than the patch tests. It seems as though the question of repeated visits, and that sort of thing, raises its ugly head here.

DR. FURCOLOW: I feel the same way as Dr. Feldmann does, that we are not ready to say that the tuberculin test is an ideal test to use but, until we can get a patch test that approximates the intermediate dose of tuberculin or 5 TU, I am unwilling to say we ought to substitute it for the intradermal. There is no question that, let us say, a majority of people with tuberculosis will react to the patch test; but, unfortunately, some people who have it don't react; and a lot of people who don't have any evidence of contact with tuberculosis will give you something that can be interpreted as a reaction. This is the crux of the difficulty so, if you retest the so-called positives to the patch test, you still don't cover what is called the negative error of the test.

DR. BOUCOT: Did you have a comment to make, Dr. Feldmann?

DR. FELDMANN: I wanted to bring up another statistical point that is important, I believe, in connection with physicians doing tuberculin testing on patients. If you go back to these risk rates that we were talking about a little earlier, they are actually in the range of, say, one to five per thousand. That means that, if a physician tests all of his patients with the idea of finding cases, he may go a long time before he finds a case and he will be unhappy about it in spite of the fact that that may be a fairly high-risk group as we would determine it on rates of a thousand. I think, then, the thing that Dr. Badger said is very important, that this has other uses besides finding cases. It is also the exclusion factor.

DR. BOUCOT: Dr. Chapman asked a question about this annual tuberculin testing in children to see when they convert. After they convert how long should they be followed? We get into the matter of whether they are treated or not treated, Dr. Chapman. Does anyone want to speak to that?

Dr. Lincoln, how long do you follow your converters? Forever?

DR. LINCOLN: We say, in the Tuberculin Committee of the American Academy of Pediatrics, that you should start testing as soon as

possible, test as frequently as possible until the age of three, and once a year thereafter; and once you get a positive test, continue to follow that child.

DR. BOUCOT: When you follow this child who converts, do you X-ray this child every six months or once a year? Is that part of your follow-up?

DR. LINCOLN: You X-ray as soon as you find conversion. If you see nothing on the X-ray and you get a good X-ray, I would think you would re-X-ray, possibly in a year and, depending upon the age of the child when you first found the conversion, at infrequent intervals thereafter.

DR. BADGER: I would like to add one word in regard to the appearance of tuberculous lesions following the conversion of the tuberculin reaction. In our nurses at the Boston City Hospital, 85 per cent of the new lesions in those who converted to positive occurred within two years of the time when the tuberculin reaction converted. The next 15 per cent of those cases occurred over the next fifteen years. So there was a great deal of difference in an area of relative security, as far as that is concerned, in that age group which is probably a little different from the infants you are talking about.

DR. BOUCOT: The hour is growing late. We know you all want to get ready for the dinner and we would like to have the distinction of having closed two minutes ahead of time. Dr. Hart has passed along a question: "Can I say something about depot tuberculin tests?" Indeed you may.

DR. D'ARCY HART: I thought the assembly might be interested in some recent work by Dr. Pepys in my unit on depot tuberculin tests, a word that has been used for some time, but is being applied in a rather special way. A paper has just come out in the journal *Tubercle* and most of you may not have seen it.

The Heaf application tool is being used to apply to the skin a cream containing PPD which produces a reaction which causes no trouble at all, but which probably corresponds to a rather high dose of tuberculin. Now, I know the question of nonspecificity will come in, but I think, under the circumstances in which it is being used or at least experimentally being used, it probably does not apply.

I will get to the most interesting example of this point. A group of nurses, aged eighteen, nursing beginners, were taken. They were all negative to this test. After the test had been done, they were given BCG. In every case the reaction site then became positive. The suggestion is that, perhaps, at last one has the possibility of a "marker" for a form of case finding that, taken to its extreme, could be given to a group of infants in an area of high tuberculosis risk who were negative to tuberculin and negative to this depot tuberculin. As soon as they became infected, the depot tuberculin would register positive.

Of course, it isn't quite so simple because it has to be quite clearly decided that it is not unpleasant to have this stuff there for so long. Actually, it is probably perfectly all right. The only trouble so far is that the reaction tends to remain positive rather a long time. Dr. Pepys feels that in the cases in which this has happened there have been no complaints. One has to allow that the introducer of a new method is the most enthusiastic and the most optimistic, but it does seem that there is the possibility of using this sort of application as a marker. Up until now it has only been a chance matter apparently as to whether somebody who had a negative tuberculin reaction to a test done previously becomes spontaneously positive associated with an infection. In these cases it looks as if it happens in the great majority of the instances.

DR. BOUCOT: Thank you very much. I am very naive. I can't understand, if the material stays there for a matter of years and then spontaneously you have a positive reaction, why the lesion doesn't remain indefinitely as long as you are positive.

DR. D'ARCY HART: The test gradually fades, but it takes several months instead of a few days.

DR. BOUCOT: If the hour weren't so late I would like to pursue this a little further, but I think we must ask the panel members certain questions. We were in fairly good agreement about the virtues of mass chest X-ray surveys, but there are two questions we must ask: Are we in agreement that the tuberculin test is of growing importance with the decrease in clinical

tuberculosis, which is a very slow decrease indeed and which we don't want to exaggerate on this panel? But are we agreed that, for mass tuberculin surveys, the 5 TU in this country, or its equivalent elsewhere, is advisable; that we do not feel that individual syringes and needles are essential in areas of high prevalence, but that we do endorse the stand taken by Dr. McDermott that, in low prevalence areas, it would be preferable to use separate syringes?

May we poll the panel members? Dr. Hart, would you go along with that statement?

Dr. D'Arcy Hart: A whole lot, but some disagreement.

Dr. Boucot: Take exception to those points or portions you don't like.

Dr. D'Arcy Hart: I don't think I can remember all the points.

Dr. Boucot: Has anyone a better memory than Dr. Hart? We had better start rapidly to go over the whole situation and see if we can come to agreement item by item.

Are we in agreement that there is an enhanced role for tuberculin testing? Any exceptions to this? (None)

Are we in agreement that in areas of high tuberculosis prevalence the single syringe with single needle and flaming in between tests is acceptable? Any exceptions to this? (None)

Now, here is where I think we are going to get the exceptions, Dr. McDermott, and I think that maybe most of the panel are not as far-seeing as the professors of Preventive Medicine: Are we in agreement that in areas of low prevalence it would be wiser to use separate syringes with separate needles?

Dr. Furcolow: These are the very areas where you have to test a lot of people to get one positive reaction and, therefore, your yield is lower and you require more mass testing rather than less. Until such time as the dangers have become more apparent, actually it would seem to me foolish to restrict in those areas. I would rather see it restricted in the high incidence areas where its usefulness is limited now, as has been demonstrated in Boston. Where you have a high prevalence of positive reactions, the follow-up of such reactions yields very little. It is only in the lower areas that this method appears to have promise.

Dr. Boucot: We were lifting our sights to the world scene and following Dr. Holm's idea that we have to do BCG vaccination in the children in these high prevalence areas and, therefore, we have a two million per month program going on.

Dr. Furcolow: In either case I would think that there is no reason to separate them into groups, as far as I am concerned.

Dr. Boucot: There is obvious difference of opinion among the panel members on this point. Is there any point in regard to tuberculin testing that any panel member would like to raise before we close?

Dr. Sommer: There is just one thing that I am sure is obvious to everyone, but it ought to be mentioned. In the mentally ill we are using I believe the tuberculin test, which is so often positive in our patients, to test our control program in the hospital. It has been often alleged that the mental hospitals are overrun with active tuberculous patients. I know we have a good number of them in our own institution. Most of our active patients come from outside, both from hospitals for tuberculosis and from other mental hospitals; and those patients are, of course, isolated and treated as those that we discover ourselves.

We are using it and I think a very important use is to test our control program and to see whether or not we are developing cases of tuberculosis by cross-contacts with undisclosed cases and with personnel, and so forth.

Dr. Boucot: I think that is a very important point, and all the panel members must be agreed on that.

Did you have anything else, Dr. Hart?

Dr. D'Arcy Hart: I reserve the privilege not to limit myself to a single test of 5 TU, but to go on to 100 TU under certain circumstances, which is done quite widely still in my country.

Dr. Badger: The only reason we don't really do that here so much is because with the 5 TU unit we avoid the false positive reaction so far as tuberculosis is concerned, and those of us who are using it as an exclusion test go on routinely to the 100 TU unit to rule out tuberculous infection. The negative test on that score is excellent but a positive test on that score in certain areas of the country may not actually mean a completely negative test.

DR. D'ARCY HART: I am glad of your second instance. As far as the first, I don't want to get into an argument about nonspecificity in Britain versus the United States. It may well differ.

DR. BOUCOT: We have avoided a number of controversial areas. Dr. Furcolow was all ready to discuss cross-reactions, but time has gone on apace and we hope that the audience is happy about our conviction that tuberculosis case finding needs to be expanded, not reduced, in order that the cases we find may be minimal in stage instead of far advanced.

Thank you to all the panel members.

PANEL FIVE

Panel members, left to right: Frederick C. Kergin, Louis R. Davidson, Norman J. Wilson, James W. Raleigh, J. Maxwell Chamberlain, F. Ronald Edwards, Nicholas D. D'Esopo, William Tuttle, Georges Canetti, Carl Semb

PANEL FIVE

SURGICAL ASPECTS OF THE TREATMENT OF PULMONARY TUBERCULOSIS: THE TYPE OF OPERATION, RELATIONSHIP TO CHEMOTHERAPY, TO BACTERIOLOGIC STATUS, TO PATHOLOGY OF TREATED TUBERCULOSIS

Chairman: J. Maxwell Chamberlain
Introducer: F. Ronald Edwards
Panelists: Georges Canetti
Louis R. Davidson
Nicholas D. D'Esopo
Frederick C. Kergin
James W. Raleigh
Carl Semb
William Tuttle
Norman J. Wilson

Dr. Chamberlain: I would like to begin this morning's session by complimenting Dr. George Sommer and his committee on the selection of the panel for this morning's topic. It should prove to be a very educational and probably exciting morning.

First of all, you are probably aware of the fact that this program is completely unrehearsed and any similarity of this panel to any of the other panels is strictly unintentional because, as you can see, we have this panel dominated by surgeons who are always complete individualists. My role as moderator is perhaps a dual one. I rather consider myself a catalytic agent to perhaps stimulate discussion; and if I become too successful in my stimulation, I will become a referee and settle the argument.

I would like to introduce the members of the panel as I know them.

The first of the foreign visitors is Professor Semb, who is a pioneer, as you all know, in thoracic surgery. He is the founder, designer, and principal agent for the Semb thoracoplasty. I knew him first in 1936 when he came over to visit Dr. Churchill in Boston at the Massachusetts General Hospital. My contact with him then was when I said, "Would you teach me how to do your thoracoplasty?" and he said, "Yes, if you will teach me how to speak English." You will notice this morning that he speaks English almost perfectly with a slight Chamberlain accent.

You already know Dr. Canetti. He is world famous for his work on the pathology and the bacteriology of this disease. I don't know him very well. I know that he is a Frenchman, or at least a Parisian, and I think we can assume that he has other virtues for which he is equally famous.

Our senior surgeon on the panel is Dr. Louis Davidson. He is also a great pioneer. In this field he has trained many men. His thinking has been greatly influenced by one of our greatest pioneers, in my opinion, Paul Coryllos. I am looking forward to what he will have to say to us today.

Dr. Nicholas D'Esopo, a long-time friend of mine, is known in many circles as the "target-point" man. He is a surgically-minded physician at times, and I think he is thoughtful and realistic, but very stubborn. I think he was assigned to this panel to lend balance to any excessive surgical optimism.

Dr. Frederick Kergin is considered by American thoracic surgeons to be one of the greatest Canadian surgeons. He has been honored in this country by most of our outstanding surgical societies, but the most distinguished honor, I think, is the fact that he is equally well thought of by his fellow surgeons at home. For us in New York this is a rather unique position.

Dr. James Raleigh was selected for the panel I suppose for two or three reasons: first, because of his profound experience in medical and surgical aspects of the disease; second, for his very clear analytic mind; and third, to defend the importance of chemotherapy in case the surgeons tend to belittle it.

Dr. Bill Tuttle is the youngest old thoracic surgeon on the panel. I simply mean that he is younger in years than Dr. Davidson, but he is old in the field. He is an early exponent of thoracoplasty and, as time went on and surgery changed, he was equally enthusiastic about resection therapy. He has a profound knowledge of both of these procedures gained at the operating table and, of course, never from books. Above all, he is a great diplomat when it is compulsory, and

I think Bill would be the first to agree that this is an acquired characteristic.

Dr. Norman Wilson is a thoracic surgeon respected by both the medical men and the surgeons. He is a profound student of the medical aspects of tuberculosis. As you know, he is associated with the Overholt Clinic. He is a surgeon of great equanimity.

Our other honored guest is Mr. Ronald Edwards, who is going to introduce our subject this morning, and he is already known to you. When I was in London this summer I knew that I would have the privilege of introducing him to you, so I asked many of his surgical friends to tell me a bit about him. I got such expressions as "topping," which translated into American means "tops," a fine chap, jolly well qualified, and a very good surgeon.

The Chairman, Dr. Chamberlain, is Assistant Clinical Professor of Surgery, Columbia University, College of Physicians and Surgeons; Attending Thoracic Surgeon, Roosevelt and Bellevue Hospitals, New York.

Dr. Chamberlain: Mr. Edwards is going to introduce the topic: "Surgical Aspects of the Treatment of Pulmonary Tuberculosis: the Type of Operation, Relationship to Chemotherapy, to Bacteriologic Status, to Pathology of Treated Tuberculosis."

Mr. Edwards: It is my duty this morning to present these problems of surgical treatment as I see them, and I am proposing to be a little different from the previous opening speakers inasmuch as I would like to present the various problems as I see them and also put in just a few words of my own experience or the experience of my colleagues (my immediate colleagues, that is) because I don't wish you to think that I am speaking for everyone from home because, just as in your country, there are still very valid differences of opinion upon the type of surgical treatment which is most appropriate for any given condition.

The advent of chemotherapy, of course, completely altered the surgical picture of this disease. Where previously the place of the surgeon had been to put the diseased lung into such a position of relaxation and rest that the natural process of healing would be assisted, it now became possible to remove those foci in which ultimate healing was doubtful. Chemotherapy by its bactericidal and bacteriostatic effect not only brought the whole disease process into a stable state more rapidly, but greatly reduced the dangers of intrabronchial spread and pleural soiling during surgery.

In 1947 the advantages of this method appeared to our group to be so paramount that we decided to switch over to resection as the method of choice, and this operation has been used subsequently by us in over 90 per cent of the patients with pulmonary tuberculosis undergoing major surgery. Other centers in Great Britain tended to be more cautious in their approach, and thoracoplasty was extensively practiced for many years after this date.

In 1953 a combined committee was formed, of which I was a member, by the British Tuberculosis Association and the British Society of Thoracic Surgeons, when all the operations done in the British Isles between April, 1953, and March, 1954, were collected and correlated by a central office; this gave the combined experience of some seventy thoracic surgeons. The cases were 8,236 in number, and it turns out that half of these were resection and half were thoracoplasty. This has given a very important group of cases which are being statistically worked out and followed up very carefully, and I think we will possibly get some indication of the answer to that thorny problem of collapse therapy versus resection.

In 1957 figures were collected by Dr. Houghton of Hatfield, a member of the same committee and, as a matter of interest, they showed that 83 per cent of the major surgery of tuberculosis in Great Britain was by resection.

Has resection turned out to be a safe operation? We have done more than 2,000 resections, and our mortality figure has been 1.71 per cent. There have been discussions as to what is the best type of case for resection and for thoracoplasty. We have taken the view that all forms of tuberculosis, open cavities and closed cavities, et cetera, should be treated by resection.

I was interested early in these controversies about the treatment, and it was said that for a cavity of the apex of the lower lobe the ideal treatment was resection, and for a cavity of the apex of the upper lobe the ideal treatment was thoracoplasty. I just couldn't follow the logic of that at all, and we maintain in our group that what is good for the lower lobe is good for the upper lobe; and I don't think we have had any

particular reason to doubt our own particular reasoning.

In the early days we resected a lot of caseous nodules, but we found, I think, with the increased or the prolonged time of chemotherapy now that it is probably unnecessary. We still remove, as I said yesterday, large ones; anything over about an inch in diameter. We feel that they are possibly potential dangers or possibly they will empty out into the bronchus and leave an open cavity.

When is the tubercle bacillus dead in these nodules? More recently people say, "We can see just the odd few tubercle bacilli," and when we ask "Are they dead?" they say, "They won't reproduce." I still think (my bacteriology may be a little weak) that, if you can stain a tubercle bacillus and if it can look like a tubercle bacillus, it is probably dormant and one of these days, like Sleeping Beauty, will wake up again or the possibilities are there for it to wake up again and produce further trouble.

Of course, one of the greatest advances of chemotherapy has been in the treatment of tuberculous empyema. The change in this picture has been quite dramatic when we compare the present operation with the unfortunate lot of such a patient fifteen years ago with drainage and thoracoplasty and a subsequent long ordeal with the draining sinus.

Now, the problem of space-reducing thoracoplasty after resection: how necessary is this, or is it not necessary? I think the answer depends upon your view as to whether a hyperexpanded lung predisposes to the reactivation of any contained foci within that area. That was hinted at by one of the previous panels, but I don't think it was taken very far.

We went into this problem somewhat. We believed that studies of the patients returning with reactivation of the disease showed that the majority developed reactivation in the hyperexpanded portion, and this is usually a portion of lung such as the apical lower segment in which a few tiny nodules had been felt at the time of operation and judged quiescent and healed.

It was our opinion that, in considering all of the residual foci of disease visible roentgenographically which might possibly reactivate in a given case, this high incidence in the hyperexpanded portion was of some significance. We followed up groups of cases over the years. Previous to 1951 we had done our lobectomies without any thoracoplasty at all. Subsequent to 1951 we did our lobectomies with thoracoplasty.

During those years I don't think our indications changed particularly as to the type of disease we operated upon, and it was interesting to see that in three years, in the cases in which we did lobectomies without thoracoplasties, we had a reactivation rate of 9.8 per cent, and in the cases in which we had done thoracoplasties, it was 3.5 per cent.

As for as the segmental resections were concerned, doing them with or without thoracoplasty didn't seem to make any particular difference to the reactivation rate. Reactivation with us means not necessarily a positive sputum, but any change by which the chest physician following that case roentgenographically, clinically, or bacteriologically thinks there has been even the slightest regression.

As to the final results of resection, I think we just have to define what is a good result in surgical treatment. A good result in surgical treatment really can only be assessed after five years. If a patient is fit and well, doing his usual work, and "bacillary negative" for a period of four years ending at least five years after operation, he certainly has achieved a good result. Also, he has got to be able to earn his living without being a respiratory cripple.

In our series we have 399 patients whom we have followed up from five to nine years, and at five years 87 per cent were well and 7 per cent had evidence of disease; so we can say that we had failed completely in 7 per cent. Also in that period 7 of those 399 patients (2 per cent) had died, excluding the postoperative deaths.

One of the most significant findings of the British review was the fact that the presence of positive sputum in the three months prior to operation had a significant effect upon the immediate morbidity, the late morbidity, and mortality. Just to give you figures once again: The spread of disease in the two-year period was twice as common in those who had had a three-month positive sputum prior to operation; the deaths were 4.7 per cent at the end of two years in those with positive sputum, and 2.2 per cent in those with negative sputum prior to operation; and the total "recoveries" at the end of two years (and this review has only been really worked out for two years so far) was 78 per cent in those who

had positive sputum prior to operation and 87 per cent in those in whom sputum had been negative for three months.

Just one or two other points about resection. We had the impression that operation under the age of twenty was associated with a higher or increased reactivation rate, but this actually was not so. The figure was exactly the same as with our general line, that is, our reactivation rate in our resection cases (any form of reactivation) during the five years is 14 per cent; and some 14 per cent of all cases have shown some sort of activity. But, finally, we have only 7 per cent active at the end of five years, so we have succeeded in dealing with those reactivations either by further chemotherapy, sometimes by another slight thoracoplasty, and making them well. Incidentally, the reactivations, curiously enough, occurred most frequently in the third year following operation.

In the fifty- to sixty-year age group we have found that resection is less well tolerated, and we got into more trouble, particularly with empyemas. It is a very chronic form of disease at this age and probably better treated by resection, but often we take what we feel is probably the easiest line and do a thoracoplasty on them because we feel that some of these "old boys" just won't tolerate an intrathoracic operation.

Has the therapeutic thoracoplasty really become an outdated operation? Professor Semb is over here and I think we should have his views on that.

As to extrapleural pneumothorax, I have no good to say of that. I think it is just a temporary procedure and can get you into an awful lot of trouble.

The question of surgery in bacterially resistant cases is now raising its ugly head more and more. So far we have in totally drug-resistant cases, that is, resistant to the three major drugs, gotten by using the less effective drugs, such as viomycin, cycloserine, and oxytetracycline. We have not had any increase in complications in these cases so far, but perhaps we have been lucky. I tell my staff that I don't know the future in these cases and certainly they mustn't lose any ability that they have in performing collapse therapy because we may be required to do this in the future. I don't know.

Steroid therapy with us has become a considerable problem from the surgical point of view because patients who have steroid therapy within even six to twelve months prior to an operation are still in an unbalanced state from the point of view of their suprarenal hormones. We have had a number of patients who had not told us that they had had steroid therapy. We've done the operations, and then the patients have gone into a very difficult, almost irreversible, hypertensive state about twelve to twenty-four hours after operation.

I think it behooves all physicians, if they present a case to a surgeon, to put in large letters on the front of the case notes whether or not there has been steroid therapy to warn the surgeon so that he can cover the operation with steroids. The operation can be covered perfectly well. It is important to start about a week beforehand and build up the dose, carry it through, and then gradually taper it off to prevent that very serious hypertensive state which might be fatal.

The question of how far we should go with respiratory function tests: Do we need, for instance, to do bronchospirometries on every patient as a routine, or are we satisfied with the more simple tests?

Bronchograms, I think, are interesting because they often produce a "red herring" in the form of errors of bronchiectasis, and the surgeon has to try to decide whether he should remove that particular odd focus of bronchiectasis which is demonstrated or whether he should just leave it alone. I think it is necessary to fit those bronchograms in with all of the previous X-rays and try and assess by a clinical examination also whether there is possibly some residual activity in that area. In our view bronchiectasis per se is no indication that the focus should be removed.

When is a lesion sterilized? Should an apparently sterilized thin-walled apical cavity be removed? Is it a cavity or is it an emphysematous bulla? Can anyone tell us how to tell the difference in these cases? I find the questions difficult to answer. Certainly, when our pathologists send back a disturbing report to say they can find no histologic evidence of activity, we review the case again with the physician and we usually come to the conclusion that, on the evidence available preoperatively and in the light of our past experience of recurrence in the long run in such cases without surgery, we would still recommend surgical treatment.

At the moment we are still judging the future course of the disease by our experience in the days of short or moderate courses of chemotherapy, and it is too early for us to say what the long-term results are going to be and how to compare them with surgery. But certainly with us the number of cases presented for surgery has declined remarkably compared to five years ago. The male surgical tuberculosis ward is almost a geriatric ward, and you try and battle to remove these chronic foci of infection.

As to the future of surgery, what is it going to be? Are we just going to have to remove some damaged bits of lung which are open to secondary microbial invasion? Is the physician going to be able to kill all of the tuberculous aspect, or will nature fight back and render the physician helpless with his drug resistance and will he come once again to appeal to the surgeon for his help?

The circumstances under which we may have to perform surgery with total drug resistance may be much less favorable than they are today, and I find it quite impossible to give any sort of considered judgment as to what the future place is. I hand this problem and the other problems that I quoted over to the panel.

DR. CHAMBERLAIN: Thank you, Mr. Edwards. It is a beautiful outline of the subject. It is going to be difficult to give you the various opinions of the panel in the remaining two hours, but we will do the best we can.

I have taken notes on Mr. Edwards' outline and will try to cover as many of his points as possible. I thought we might begin by considering the two major surgical procedures, namely, thoracoplasty and resection. First, I should like to call on our pathologist, Dr. Canetti, to describe to us what the role of the bronchus is and was in the patient who has had a thoracoplasty, before antibiotic therapy and after antibiotic therapy; and also the role of the bronchus, intramural disease, and so forth, in patients who have had resection, and what influence antibiotics have had perhaps on our surgical results.

Do you understand the question, Dr. Canetti?

DR. CANETTI: Yes, I understand that you are asking me a very difficult question.

Let us first speak about cavity and bronchus under thoracoplasty. I must confess that, as far as I know, there is rather little information on that because few patients who have had thoracoplasties have undergone resection, so that you just don't know what has happened to the cavity and to the bronchus and, of course, a few patients have died. We have rather few studies on cavities under thoracoplasty. There are a few, but not many.

I would perhaps extend the subject to cavitary healing under collapse therapy, which is not very different, and say this: that the main feature under collapse of cavitary healing, under collapse therapy, was that the cavitary healing occurred with bronchial closure. There are two main types of cavitary healing, one with inspissation, that is, with a remaining necrotic portion, which was by far the most frequent; and the other healing, which was less frequent, was the healing without any necrotic remnants, that is, the transformation of the cavity into a real fibrotic scar (shrinking and transformation). These were the two types of healing.

In both of them the bronchus usually closed; but sometimes, especially in the second type, the type of scar transformation without necrotic remnant, the bronchus remained open.

This is a very broad picture on cavitary healing and the state of the bronchus under collapse therapy. Again, I must state that the number of cases in which this has been studied is few, and what is even far more important in my mind is that bacteriologic studies on cavities healed under thoracoplasty, without chemotherapy of course, are so few that they are almost nothing.

If we come now to cavitary healing under chemotherapy, here we stand on very sound ground because extensive studies have been done in several countries and I think I can summarize things like this. There are two main types, as you know, of cavitary healing under chemotherapy: the one, healing by inspissation, that is, by disappearance of the cavity as the cavity fills with necrotic remnants; and the other type is the one you know as open-healing. Open-healing means that the cavitary space has remained, but that the sputum has become negative.

As you know, the second type of healing, which used to occur very seldom without chemotherapy, has greatly increased in frequency. To give you a sort of broad statement about the relative frequency of both types of healing: Among 639 cavities, 323 were not healed and 308 were either inspissated or cleansed, that is, healed or close to healing. Among these 308 there were 209 which had healed by inspissation and 99 which had

healed by cleansing; that means the cavity remained as a cavity, but there were no necrotic remnants in the cavity.

Although the proportion of open-healed cavities has greatly increased, still the cavities healing by inspissation, that is, with necrotic debris and shrinking of the cavitary wall around this debris, is far more frequent. The proportion is more than two to one.

In these two types of healing, what is the state of the bronchus? I think that is the sort of question you want me to answer. In the inspissated cavity one very important fact was shown early in 1952 by Dr. Auerbach and his team. Dr. Auerbach has shown that under chemotherapy it happens that the bronchus remains open although the cavity heals by inspissation. As I told you before, this was a very unusual fact before chemotherapy.

Now, this is absolutely true. We see, far more often than before, open bronchi in inspissated cavities; but I must stress that, although this happens far more frequently than before, yet the closure of the bronchus under chemotherapy, the inspissated cavity, is still the more frequent event.

In my material I have dissected the bronchi in 126 inspissated cavities. Those which are eliminated from these statistics are only the very small ones, less than 10 millimeters, and you just can't have a good dissection of the bronchus. These, then, are mainly cavities greater than 10 millimeters in diameter, which is still rather small. Among these 126 inspissated cavities, in 37 per cent of the cases the bronchi were open and in 63 per cent of the cases the bronchi were closed.

Again, I must stress that Dr. Auerbach has been perfectly right in stressing the fact that the cases in which the bronchus remains open are far more frequent than before the days of chemotherapy, but still the closure of the bronchus is more frequent nowadays. This is for inspissated cavities.

For cleansed cavities, that is, for open cavities, we have a very different situation. Among 67 cleansed cavities in my material there are just two-thirds, or 67 per cent, which had open bronchi, and 33 per cent which had closed bronchi. Of course, what is expected is that the bronchus is far more often open in these cavities, and this is what really happens. The astonishing fact about these cleansed cavities is that in 33 per cent of the cases the bronchi were closed. This is perhaps not very easy to understand and I don't understand it myself entirely; but the fact is that in a good proportion of cleansed open-healed cavities the bronchus is closed—in one-third of these cases to be exact.

I should add that all of these bronchial closures of which I am speaking in both kinds of cavity are by fibrotic stenosis. I don't speak of temporary closure by caseous plugs or by calcification, or such things. This all happens, but I am speaking of fibrotic stenosis, which is the main mechanism.

Should I say a word about bacterial content?

DR. CHAMBERLAIN: Let me ask you this question; I want to get to the practical aspects of the problem. From your studies do you think that the thoracoplasty procedure should be more effective or less effective as a result of chemotherapy? In other words, are the mechanics of thoracoplasty going to be influenced by the fact that there is re-epithelization of the broncho-cavitary junction or not? Do you think thoracoplasty is going to be more effective now because of the nature of the bronchial healing, or do you think it is going to be less effective? In a moment we are going to ask Dr. Semb for his results.

DR. CANETTI: I think that there is no reason why thoracoplasty should be less effective. Either the cavity is more or less healed and there is then no need of thoracoplasty; or the cavity has failed to heal for any reason (bad chemotherapy or something like that) and then I don't see why thoracoplasty should not give the same results as before.

Thoracoplasty probably works in several ways: one, on the bronchus; and, two, by changing the intercavitary conditions, blood supply, and all that. So I can't see why thoracoplasty should not have the same effectiveness after chemotherapy, if, of course, thoracoplasty is needed.

DR. CHAMBERLAIN: Do you have anything to add, Dr. Auerbach?

DR. AUERBACH: I have just one or two things I would like to add. I agree completely with Dr. Canetti on the pre-chemotherapy closure of cavities as to its method, except that we were impressed with the fact that even in the radial scars we saw closed bronchi, scarred bronchi, leading to these closed cavities.

On post-chemotherapy closure, I would just like to say that I think the difference in Dr. Canetti's finding more cavities closed may come from the fact that we have had an opportunity to do serial sections on the cases in which we could

not probe a bronchus into the cavity. In the serial sections we were able in all instances to prove the opening of the bronchus into the cavity, the inspissated cavity.

Just one point, if I may continue on the prediction. When we discussed the re-epithelized bronchus as the bronchial cavitary junction under chemotherapy back in 1952, we made a prediction that thoracoplasties after chemotherapy would not be as successful as they were in the era prior to chemotherapy for the reason that the success of a thoracoplasty in the pre-chemotherapy era was due to an ulcerated bronchus at the bronchial cavitary junction.

One of the earliest things that happens under chemotherapy is a re-epithelized bronchus and, therefore, the prediction we made (and we have no reason to go back on that statement) is that you would not get the same uniformly good results following chemotherapy because you can't knit re-epithelized surfaces.

DR. CHAMBERLAIN: Dr. Davidson, what would Paul Coryllos have thought of this and what do you think of it insofar as the practical aspect is concerned? Will thoracoplasty be better or worse?

DR. DAVIDSON: I think, unfortunately, Dr. Coryllos would be just about as confused as we all are. I feel this meeting has been a splendid one because of one particular condition, and that is that the entire confusion is better organized.

I feel that both Dr. Coryllos and Dr. Auerbach at Sea View Hospital, long before the advent of antimicrobials, very definitely established, to our minds at least, that the bronchocavitary junction was a very important anatomic part of the entire configuration because it was that part of the anatomy which was altered and permitted through various mechanisms to have the cavity closed.

I take one point of issue with Dr. Auerbach's statement, and perhaps this point will be developed later. In these open-healed cavities, the characteristics of which we will go into later, I do not think there is any need for surgery.

DR. CHAMBERLAIN: When I was in Oslo a few years ago, Professor Semb showed me some very interesting X-rays. Could you say just a word, Professor Semb, about the mechanism of cavity closure under thoracoplasty and tell us the answer as to whether the results are better now than they were prior to chemotherapy.

DR. SEMB: We now enter into the question of the physiology of a thoracoplasty, more or less, and it is very difficult and complex. As far as the question of whether the thoracoplasties are getting better results after chemotherapy than before, I am convinced that the results are definitely better now than they were before.

With respect to the question of the closure of the cavity by thoracoplasty: We have always been more or less convinced that the theory of Coryllos had a lot of truth in it. With tomograms of the patients before, after, and during treatment with thoracoplasty, we have tried to visualize the draining bronchus of the cavity; and it can be done in at least 78 per cent of all of the cases.

There are two types of bronchi. There are the long thin bronchi and the short, wide, and stiff bronchi. We always use this method: After thoracoplasty, we try to find out by means of a tomogram two or three weeks after the operation whether, through the collapse, the draining bronchus and the cavity have closed. If you can find that and demonstrate it (and you can in most cases), then we feel sure that the end result will be sufficiently good at least in 90 to 95 per cent of the cases. A reopening of the draining bronchus will practically not occur. In those cases in which we cannot close the draining bronchus by a thoracoplasty, we expect a relapse to occur.

These experiences, I think, speak in favor of the theory of Coryllos. Naturally, many other factors are actually in these questions, but we don't know too much about them. But we know that thoracoplasty also has an excellent influence on the smaller and medium-sized, and even the larger bronchi. In what way, we cannot really tell.

Besides, we are faced with the fact that there are in most cases also nodular infiltrations not only in the affected lobe, but in the other lobes and even in the other lung; and one of the results of the thoracoplasty, I believe, is to support resorption and healing of these nodular infiltrations outside the main focus and even in the lower lobe and maybe also in the other lung.

DR. CHAMBERLAIN: Dr. Auerbach spoke from a theoretic standpoint. He thought it would be less effective and, when I saw his original work and saw the re-epithelization of the bronchocavitary junction, I agreed with him. But Dr. Semb, who has had more experience with thoracoplasties than any of us, says that the results are even better; so I think we can close this aspect of the surgical subject by agreeing with Professor Semb, whose experience is much greater than

mine and perhaps than that of most of us at this table, especially since the introduction of chemotherapy.

Let us go on to a very important subject that was touched on in the panel yesterday: How long should we give these antituberculous drugs prior to surgery? I would like Dr. D'Esopo to open the subject. Dr. D'Esopo, just briefly tell us how long you think we should treat these people and then we'll start an argument.

DR. D'ESOPO: First of all, when chemotherapy is started in the case of tuberculosis it is not known whether the patient is going to come to surgery, so we really have two ways in which this question can be answered. I think what you want me to discuss is the case that is certainly from the very start earmarked for surgery, an individual whose disease is limited to the lobe on one side, who has a very large cavity and the sort of thing that in our experience will almost never close with chemotherapy alone—the case that from the very first day seems destined to have surgical treatment.

We treat these patients until they become noninfectious. I don't think this is entirely necessary. I think the complications are certainly related to the susceptibility of the organisms to drugs rather than to the state of sputum at the time of operation. People such as Dr. Wilson operate on these patients when they are still positive. He says there are no complications or very few complications, and I have every reason to believe him.

On the other hand, I think it is perfectly safe to treat these patients with chemotherapy until they are noninfectious or until the number of organisms in the cultures is very low.

DR. CHAMBERLAIN: Yesterday Norman Wilson took the attitude that these people could be treated quite early. Dr. Wilson, will you defend that proposal?

DR. WILSON: I want to make it clear that I am not advocating premature resection. I have been quoted many times as advocating that, but I am not. But I do think it is equally important for us to have criteria which we can abide by to guide us to surgery just as the medical man has studied chemotherapy and has evolved rules and guides that he is following.

The important question here is, I think, to put it in fundamental language: Do an open cavity and positive sputum create a danger to the patient undergoing resection? That is the fundamental issue. I would like to bring out this fact because this has to do with what I am going to say. Differentiate between an open cavity and a positive sputum under effective chemotherapy in contrast to an open cavity and a positive sputum in spite of prolonged chemotherapy. In one place you are operating on a well-protected patient, and in the other you are operating on a patient who is completely out of protection of the major drugs.

In 1951 and 1952, as you know, Dr. Chamberlain, we operated on 232 patients under original chemotherapy, and 108 of these had had either no preoperative chemotherapy or had had it for less than a month. I would like to emphasize also that this was not indiscriminate surgery. These people had to meet surgical criteria, which means that the only offending lesion was in the unit of lung that was to be "thrown in the bucket." The people who had uncontrolled disease in other portions of the lungs took longer to prepare for surgery. We all admit that. But once the patients meet surgical criteria, our statistics show that the earlier you do your surgery, the less tuberculous morbidity you have. The earlier in this series it was done, the better the results.

DR. CHAMBERLAIN: That is very interesting because from your discussion I would conclude that, since you are not leaving behind any active disease or any known active disease, the sooner you can get the lesion out of the body, the better, especially when the drug is still efficient. On the other hand, I would like to know about the other countries. Professor Semb, do you have a special routine you follow in preparation of these patients prior to resection?

DR. SEMB: As I told you yesterday, when it is a question of resection, we give a pretty long preoperative treatment with antibiotic drugs, at least four to six months. It is more important to have the preoperative treatment in the resection case than in the thoracoplasty case because of the difficult question of complications.

We know from the old times that we can do thoracoplasty pretty safely without any chemotherapy beforehand; but naturally it is of great importance to have it, especially to avoid the spread of disease. We can do a thoracoplasty more safely in cases in which we have positive sputum even after preoperative treatment. If we have drug resistance, we prefer a thoracoplasty as a less dangerous procedure than resection.

DR. CHAMBERLAIN: Mr. Edwards, do you agree with Dr. Wilson?

MR. EDWARDS: Well, sir, I find his views quite startling and I have been brought up in the school, as I think I said yesterday, in which we like to do our resections after very long periods of chemotherapy. I rather feel that Dr. Wilson is looking at the cavity and he is shutting his eyes to what else is going on in the lung, even though it is going on but you can't see it on X-ray. I find it very difficult to believe that a patient who has had only two months of treatment, with disease of unknown duration, who has been ill, can have the rest of his scatter disease (which, as I say, we probably can't see, but which is there microscopically) under the proper influence of the drugs until he has had at least six months of treatment, and probably longer. To undertake what I, at any rate, think is a safe operation, the duration of such treatment should be that long. But Dr. Wilson's results are very interesting and very startling. Maybe our original concept is all wrong.

DR. CHAMBERLAIN: Dr. Tuttle, you are so quiet that I am a little nervous about you. Would you give us your opinion?

DR. TUTTLE: I am quiet because I haven't been asked to say anything. In our experience and in our resections we have found, and our figures will show, that the incidence of complications in the patient with positive sputum, even though he has been under prolonged periods of antimicrobial therapy, is five times as high as that in the individual who underwent resection with a so-called negative sputum. It is our feeling that, while we do not shun the person with positive sputum, we look upon it as a calculated risk and we know that our incidence of complications is going to be higher in that group than it is in the group with the so-called negative sputum.

DR. CHAMBERLAIN: Let us hear from some of the medical men. Dave Cooper, what is your policy?

DR. COOPER: I belong to the school that likes a reasonable period of at least six months of chemotherapy before surgery. However, there are instances when it is logical to go ahead at an earlier date. As a rule, I would prefer a minimum of six months of chemotherapy prior to surgical interference.

DR. CHAMBERLAIN: Dr. Julius Wilson, do you agree?

DR. JULIUS WILSON: Yes, I do. I certainly agree with that in general. However, I object to this general idea of laying down a rule of, say, six months or any period of time. Each case is absolutely different. I think we fall into the trap here of thinking that Dr. Norman Wilson operates on all of his patients in the first month they are in the hospital and somebody else always waits two years. It just doesn't work that way with individuals.

DR. CHAMBERLAIN: Dr. Tucker, what is your policy?

DR. TUCKER: From the standpoint of bacteriostasis with the presently available antimicrobial drugs, particularly in the original treatment, there is no particular reason why drugs need to be given a long time. I agree, however, that the simple question of bacteriostasis at the time of the resection is not the sole answer. I really don't know.

Dr. Chamberlain, if I may, I would like to make one comment on this thoracoplasty business because (from my Minneapolis days) we have just completed a follow-up of 150 thoracoplasty cases with a minimum of seven years' follow-up. The patients were operated on in the period of 1947 to 1951. All of them met with initial success in conversion to sputum control of the disease by the usual criteria. These all had relatively short courses of chemotherapy judged by present-day standards, but all had what was then considered adequate chemotherapy.

The startling figure is that with a minimal seven-year follow-up, only 41 per cent are today successes and 59 per cent are failures. There has been a gradually climbing failure rate with the passage of years. This, of course, is quite different from what Professor Semb has been referring to.

In all justice to Professor Semb, his type of thoracoplasty was not carried out. These were carried out by thoracic surgeons well known to you gentlemen, but it was not the Semb thoracoplasty.

DR. CHAMBERLAIN: I don't suppose anybody has a better follow-up than exists in the Scandinavian countries. As you all know, their system is such that they get 100 per cent follow-up on all of their cases.

DR. NORMAN WILSON: I want to back up what Dr. Julius Wilson said. It takes me eight months to decide to operate on some people. But I think it might be helpful if we would specifically ask: If you have a twenty-four-year-old man or a

twenty-six-year-old man with a cavity in his right upper lobe and no visible disease elsewhere, are you going to condemn him for eight months of his life while you make up your mind that he needs his lobe out? I think that's the problem. Are we treating people by prejudice or by fact?

DR. CHAMBERLAIN: I think your point is well made, Dr. Wilson. You would like to get at these people, when it is pretty well established that they are going to have surgical treatment, as quickly as possible. In this regard I always think of Dr. Churchill's statement written a very long time ago when he said that "Through prolonged hospitalization the patient's personality is often converted with the sputum." I think that is your point.

Dr. Sommer, could you add something to this?

DR. SOMMER: I would think before we go further on this thoracoplasty problem it would be worth while to ask Dr. Semb just exactly what their follow-up results are. Maybe you did intend to do that.

I would like to mention just one thing. I have a small group of patients treated in two mental hospitals who have been very carefully followed, and they don't get away from us for obvious reasons. In these cases the results have stood up very well and better than Dr. Tucker's patients perhaps because his are out on the road, where most of us would like to be.

DR. CHAMBERLAIN: I intend to get Professor Semb's statistics in just a moment.

In this section on chemotherapy I suppose we can conclude that we must individualize each case, as Dr. Julius Wilson has outlined, and that most of us would agree with Dr. Norman Wilson that, when there is a pretty clear-cut indication, we should get to surgery as soon as possible; roughly, four to six months after starting their chemotherapy.

Another point raised by Mr. Edwards in his outline was whether or not these bacteria are dead. This subject is a little bit old and we have been over it and over it, and over it again; but, in view of the fact that this meeting is going to be recorded I think we should have some record as to whether or not the organisms are or are not dead, or whether they are just sleeping.

I am just going to poll our bacteriologists and pathologists here this morning to say yes or no or very briefly, if necessary, to tell us how they feel about it. Hugh Burke, I know we can't consider you exactly a bacteriologist, but your scope is very broad and I would like to know what you think about it. Are they dead?

DR. BURKE: We just don't know. The thing that impresses me is that, as our cultural techniques improve, we decide that some that we thought were dead are now alive.

DR. CHAMBERLAIN: Dr. Froman?

DR. FROMAN: I am more or less inclined to agree with Dr. Burke. It is a very difficult question to decide. As you know, it is quite controversial. I think that, with an increase in time after sputum conversion, the bacteria in time will die.

DR. CHAMBERLAIN: Dr. Raleigh, will you give us your opinion?

DR. RALEIGH: I think the question is losing some of its spice, but I think we can say this regardless of the bacteriologic opinions about it. In a series of patients resected at Sunmount on whom the bacteriology of the resected specimen was studied, approximately one-third yielded viable tubercle bacilli in their resected specimens, that is, bacilli that could be cultured or which caused disease in guinea pigs; and two-thirds did not.

When these patients were subsequently followed, the incidence of tuberculous reactivation, that is, of relapse, was just as high in those whose resected specimens failed to yield viable bacilli as in those whose resected specimens yielded viable bacilli. In other words, from the point of view of prognosis and from the point of view of the persistence of some tubercle bacilli capable of causing relapse, this finding in the resected specimens has not yet been shown to have reliable prognostic significance.

DR. CHAMBERLAIN: Dr. Steenken, you always have very strong opinions.

DR. STEENKEN: Of course, the question of whether the organisms are living or dead shouldn't be just a frank statement that they are living or that they are dead. I think that in many of these lesions you have a normal death rate and you have a normal growth rate. So, if the organisms are in an unfavorable environment, the death rate will be greater than their growth rate; and if these organisms have been in an unfavorable environment for a long period of time there is no reason why, when they are not growing, they should not be dying off. Of course, there will be some latent organisms there.

Even with the best techniques you cannot grow 100 per cent of the organisms and, since we have

no vital staining technique that will tell us the difference between the living and the dead organisms, it is very difficult to say. However, Dr. Edwards made the statement, when you see these organisms stainable but they will not grow, that they are just little fairies lying there waiting to come to life again. I can't go along with that because we have sufficient experimental proof to show that you can lay organisms into the body (either attenuated, as I said yesterday, or dead bacilli) and find they retain their staining properties for long periods of time.

DR. CHAMBERLAIN: This has been a hobby of Dr. Gladys Hobby for a long time. Could you say something, Dr. Hobby?

DR. HOBBY: I don't think this is a good time to get into this argument again but, nonetheless, the question as stated, Dr. Chamberlain, I would say really can't be answered. Dr. Auerbach and I have felt that whether or not these organisms remain viable depends in large part upon the degree of healing of the lesion and the type of lesion, so without the pathologic description I would say the question is unanswerable. The important point to me, however, is that, if there is any possibility that the organisms may be alive, we must assume that they probably are and proceed accordingly.

DR. CHAMBERLAIN: Then I think we should accept that conclusion. You have all heard the opinions of the various bacteriologists. We will go on to the next point unless Dr. Canetti would like to say something.

DR. CANETTI: I certainly would. In my opinion, there is a very important fact which points to the fact that the nonviable bacilli which are found in several types of lesions are in the great majority of cases dead bacilli; and this fact is that there is a general trend, a sort of twofold trend which is parallel. One of these trends is toward an increasing proportion of bacilli, of all existing bacilli, to be nonviable; and at the same time the trend exists for the number of old bacilli existing to be smaller and smaller, that is, the bacilli disappear more and more.

These two trends coexist with healing of cavities and especially with healing of closed lesions. Not only do more and more of the existing bacilli shift to the group of nonviable bacilli, but the proportion of cases showing no bacilli at all increases at the same time. I have some slides here which show this well, especially in cavitary closure, but I can't go into that.

The fact is that the development of nonviability of the bacilli goes hand in hand with the disappearance of bacilli, which is more and more frequent in cases in which no bacilli at all are found. This is for me a closed argument, an important argument that these bacilli, the nonviable bacilli, are in the great majority of cases a sort of intermediate stage between viability and total absence of bacilli; that is, these are just dead bacilli which ultimately disintegrate and disappear.

Of course, this doesn't mean that if, in a very dirty cavity with an open bronchus and all that, you find some nonviable bacilli, this may not be due to certain deficiencies of our cultural technique. It may very well be the case but, as a whole, I think that in the great majority of cases nonculturable bacilli found in healing lesions are dead.

DR. CHAMBERLAIN: Would Dr. Youmans or Dr. Robson like to add anything to this discussion? They have strong feelings.

Dr. Robson?

DR. ROBSON: I would have thought that it was quite clearly established, experimentally at least, that the rate of disintegration of bacilli is extremely slow. In our own experiments over a period of seventeen months, which is quite a long period if we equate the mouse to the man, only about half of the bacilli present have disintegrated. That is the first point. Although I certainly agree with what Dr. Canetti has said, that the bacilli do disintegrate, under the conditions under which I have studied them the rate of disintegration is a slow one.

The second point is that, again on the basis of what we have done, I find it very difficult to believe that some of the remaining bacilli are not alive. Of course, one tries all kinds of methods and one has only occasional successes, but I would say (it is a very old controversy) that the onus of proof is on the people who claim that the bacilli are dead and that for practical purposes one ought to assume that a few of the bacilli remaining, even after long periods, are still alive.

I do think there is one further point, and that is that all live bacilli in lesions are not the same insofar as their capacity to reactivate is concerned. That is a point which I think everybody would accept. For that reason I think it is with older lesions or lesions which have been subjected to more prolonged chemotherapy that the possibility or probability that the few live bacilli

there might start a lesion again is less because of some certain closeness which happens in these organisms, to the meaning of which I and, as far as I can see, many other people don't have a clue.

DR. CHAMBERLAIN: You can now draw your own conclusions. I think we should go on to another point of Mr. Edwards', namely, the ancillary aids in evaluating a patient for surgery, functional studies, and so forth. This time I am going to call on Dr. Raleigh to open the discussion and then we will turn to a surgeon, Dr. Kergin.

Would you tell us, then, Dr. Raleigh, what you think the minimal requirements are and the ones that you would routinely advise in selecting a patient for major surgical procedure?

DR. RALEIGH: I think that the most important method of evaluating a patient as a candidate for resection or for thoracoplasty, for that matter, is a careful personal evaluation of the patient, an awareness of his history, an awareness of his ability to carry on ordinary exercise, shortness of breath on exertion, and so forth. I think the fact of sputum volume should be taken into much more consideration than it is. We have heard a lot about the presence or absence of tubercle bacilli and their resistance or susceptibility to drugs, but I think that the sputum volume is frequently taken for granted to this extent, that, if it is negative, there is probably very little of it. That is generally true, but complications can arise in patients with chronic nontuberculous bronchial disease, chronic bronchitis, and some of these complications can be prevented by proper attention to the presence of bronchorrhea.

With respect to tests of pulmonary function, I think they are being rather widely overdone, and the general feeling among experts in the field is that they can evaluate a patient almost as well with a stethoscope as they can with many of the instruments in the pulmonary function laboratory; as well as they can, for example, with bronchospirometry or a maximal breathing capacity.

Unfortunately, not all of us are experts, and I think it is only after considerable experience in the use of these pulmonary function tests that a physician arrives at the point at which he can do without them. In other words, their principal value seems to be to train physicians to recognize (both quantitatively and qualitatively) defects of laboratory function so readily that they can eventually do this by physical examination or, at most, by the use of a careful fluoroscopic examination.

Fluoroscopy, I think, is particularly of value in evaluating the distribution of function between two lungs, and I think that, in experienced hands, it gives about as much and as useful information as bronchospirometry. Bronchospirometry in very experienced hands does, of course, give figures that can be put on a chart, and perhaps for purposes of research, for purposes of study, comparison of pre- and postoperative ventilatory findings, and distribution of ventilatory function bronchospirometry may be justified; but as a routine procedure fluoroscopic examination will probably give you as much information.

The use of such things as careful evaluations of cardiac, renal, and other organ system situations goes, of course, without saying. I think that most patients would have those evaluated in any event.

I think one thing that perhaps should be remembered is that age itself is not necessarily a contraindication or even a serious problem in evaluating a patient for surgery. At Sunmount certainly we have no upper age limit and, of course, in the treatment of such diseases as carcinoma of the lung there is certainly no upper age limit. So, if the indication for surgical treatment is genuine and unequivocal, patients in any age group are candidates provided their pulmonary and general physiologic states are no greater risk to them than the disease for which they are being operated.

DR. CHAMBERLAIN: Dr. Kergin, what procedures do you like in the selection of patients? For example, do you think a routine bronchogram is necessary, a routine bronchospirometry or bronchoscopy? What about postero-anterior and lateral tomograms as a routine prior to resection, and so forth?

DR. KERGIN: As much as I regret it, I can't disagree with anything Dr. Raleigh has said. I think his outline is very much the one I had in mind when you mentioned my name in regard to this question.

Just to comment on his remarks: First, I would say that, like him, we believe that extensive respiratory function studies are interesting as a research project, but as a practical thing in treating patients with tuberculosis we reserve bronchospirometry and the extensive series of tests that may be used for certain patients in

whom our critical assessment would suggest there is a problem. I would say, however, that we must remember that in certain patients who have had bilateral disease we get some remarkable surprises at times. We have been misled at times on our stethoscopic and fluoroscopic examinations. We might think that one lung was a very poor lung and the other perhaps quite a good lung, when on bronchospirometric examination we have found that our assessment was quite incorrect.

Among the routine examinations which I would like to mention, I think bronchoscopy is essential in all of these patients and is an important aid in assessing the competence of a lung or a lobe. I do not believe that routine bronchography is important, not routine certainly. It is a valuable aid. Like Mr. Edwards, we find that bronchography requires a lot of judgment in its interpretation. There are many distorted bronchi in lobes which have had previous disease which are not in fact a source of danger to the patient.

About the bronchorrhea, I think one thing to mention is that at times judicious tracheostomy can be very important in those patients who have poor respiratory function and a lot of sputum which may or may not be infected with tubercle bacilli.

DR. CHAMBERLAIN: That is an excellent point, I think, and I am glad you mentioned it, Dr. Kergin. Certainly in these bad-risk patients tracheostomy may mean the difference between success and failure.

Dr. Semb?

DR. SEMB: As far as the functional studies are concerned, I think they are most important in the borderline cases and just after introduction of chemotherapy. We had a lot of patients in our country who were regarded as inoperable and the question was whether they could be operated on with the support of chemotherapy. We took up the question, and I feel that there is a field for such examinations and they must be a little more complex than usual.

The question of ventilation ability of the lung is not as important as many of the other studies. The most important is the gaseous exchange. We have a special apparatus for that with which the intake of oxygen and the output of carbon dioxide can be measured before, during, and after a certain exercise; that gives us accurate figures of the total reserve of both lungs.

Bronchospirometry is of value when we operate on cases of bilateral disease, as we do pretty often. In addition, there are studies by heart catherization of the circulation in the smaller circuit. Maybe it is of more importance in old sclerotic cases than we previously realized, and we have often found, in sclerotic cases and in cases of fibrosis and pleural exchanges, latent or manifest pulmonary hypertension, which is a serious complication; and in those cases we find we should be very careful with extensive surgery.

We also learned that that pulmonary hypertension could be released by decortication, especially if we found a bilateral empyema; and we have evidence in a couple of cases in which a manifest hypertension has become normal after such a procedure.

DR. CHAMBERLAIN: I think we can conclude, then, from this discussion that bronchospirometry should be used in selected cases and that, with increasing experience on the part of the examiner and the surgeon, probably the fluoroscope, the stethoscope, and the usual standard equipment are adequate. Surgery is not an accurate science in a mathematical sense. We may have the figures before operating, but the surgeon never knows what the complications may be. He may anticipate reducing the function by 50 per cent on one side of the body; but, if he gets pleural complications and fixation of the diaphragm, fixation of the costal breathing, he may lose total function on that side. Though we do have the figures, preoperatively, we aren't always able to predict what is going to happen postoperatively, so the preoperative figures may or may not be of value.

Now I want to get on to the most important part of the discussion. That has to do with the selection of patients for thoracoplasty or resection. First of all, before we begin the discussion I would like to poll the surgeons as to the ratio of these two procedures as practiced in their environments. Are they doing 50 per cent thoracoplasties and 50 per cent resections, and so forth?

Let me begin with Dr. Davidson. What, roughly, is the percentage at Sea View?

DR. DAVIDSON: At Sea View Hospital we are doing in the main resectional surgery, but with this addition: we feel that there is a tendency to perform more and more thoracoplasties among those patients who have cavities with resistant organisms. Here we feel, as everyone else does, that the incidence of morbidity and mortality in

the patient who has resistant organisms in comparison with the one who has not is too large to risk (for the sake of your conceit) excision against thoracoplasty.

DR. CHAMBERLAIN: Could you give us a rough figure?

DR. DAVIDSON: I would say at the present time (this is merely an impression) that we do 90 per cent excision, or maybe a little more.

DR. CHAMBERLAIN: Mr. Edwards?

MR. EDWARDS: Our experience is very much the same as Dr. Davidson's. We have been, as I said in my report here, doing about 90 per cent resections, but I think certainly in the last year or eighteen months the number of thoracoplasties that we have done has gone up slightly. This may be because of a little fear of resection in resistant organism cases, but we have, as I said, tended to do resections in those cases. Also I think it reflects a little the age of the patient. We do tend also to do thoracoplasties on the very much older age groups.

DR. CHAMBERLAIN: Dr. Kergin?

DR. KERGIN: We are very strongly on the resection side at the present time, and I think our figure is 95 to 97 per cent resections versus thoracoplasties. I am assuming that we are speaking of thoracoplasty now as a primary surgical therapy for tuberculosis.

DR. CHAMBERALIN: That is right.

DR. KERGIN: We also have had in mind that in our resistant cases perhaps thoracoplasty would be safer. I think we are fortunate in Toronto that we don't seem to have as great a problem as you have in New York; for instance, with patients coming to you with resistant organisms in the sputum. Perhaps it is because we don't have so much home treatment. Most of our patients are treated in a sanatorium on a well-controlled regimen.

Also, unlike anybody else who has spoken so far in this symposium, we do use pyrazinamide and we find it a useful fourth drug. So to date we have not had occasion to swing over to an increased number of thoracoplasties, though the time may come with the indications Dr. Davidson mentioned.

DR. CHAMBERLAIN: Dr. Tuttle, do you remember how to do a thoracoplasty? What is the percentage of thoracoplasties to resections in your environment?

DR. TUTTLE: I would say that at Herman Kiefer, which is our largest hospital, we do probably in the neighborhood of 90 per cent resections and 10 per cent thoracoplasties. In some of our smaller institutions, where the racial background of the patient is slightly different, we do even a higher percentage of resections than that. I can think of one small institution in which our percentage of resections is in the neighborhood of 99 per cent, with 1 per cent of thoracoplasties.

I don't necessarily go along with the idea of the so-called resistant strains; in other words, to subject those people to thoracoplasty rather than resection because you are afraid you are going to get into trouble. If the surgeon is afraid he is going to get into trouble, then he shouldn't be a surgeon. He should become an internist, where he can think about these things. Therefore, I don't think that is an answer.

I think there is a distinct danger also in that, if we are going to do a type of operative procedure which I consider an inadequate procedure, that is, thoracoplasty, then we may leave a lot of people running around the country with an occasional positive culture with a resistant organism. If we do that and continue in that practice, we are going to end up in a situation in which half the population is going to be infected with resistant organisms about which one can do nothing.

There are distinct dangers if one projects the problem by being afraid to do something because you know that the calculated risk is greater.

DR. CHAMBERLAIN: Thank you, Dr. Tuttle; those are good points.

Norman Wilson, what about you and the group at the Overholt Clinic?

DR. NORMAN WILSON: I can't speak for the group in the Overholt environment. I can only speak for myself. I would say that under average circumstances I do 20 to 25 per cent thoracoplasties and 75 to 80 per cent resections; and I would like to bring out the point that I think it is meaningless what percentage you do. I work in two institutions and my percentage is entirely different in the two places because I get different sorts of lesions to work on. The more advanced disease I get, the more thoracoplasties I do.

DR. CHAMBERLAIN: Dr. John Steele, can you tell us not only your own experience, but do you happen to have any information from the Veterans Administration as a whole?

DR. STEELE: Yes, I have recently been tabulating the surgical operations in some thirty VA hospitals. Thoracoplasties are running about 10 per cent and resections 90 per cent in that group of thirty hospitals. In some hospitals no thoracoplasties whatsoever are being performed. Included in the thoracoplasties, of course, are extraperiosteal plombages. In our own hospital we are running about four to one resections to thoracoplasties, but we do have a high percentage of salvage patients.

DR. CHAMBERLAIN: Dr. Mulvihill, do you have a percentage in the environments where you are working?

DR. DANIEL E. MULVIHILL: I would say that my percentage would be in general agreement with those that have been given already. I agree with Norman Wilson that a lot depends on the material with which you have to deal in the various institutions. I would say generally that in the institutions with which I have to deal there are 90 to 95 per cent resections. Thoracoplasty is used only for a very special indication.

DR. CHAMBERLAIN: Professor Semb?

DR. SEMB: The reason why we do as many thoracoplasties as we do is that from our experience the results are good, last very long, and we have control up to ten to twenty years with a very small percentage of relapses. The other reason is that we feel it is a more physiologic operation as far as the effect, not on the cavities, but on the nodular infiltrations in the other parts of the lung and the reduced elasticity of the lung tissue. I feel in all there is an indication for both, naturally, but we do 72 per cent thoracoplasty and 28 per cent resections.

DR. MULVIHILL: Could I ask Dr. Semb what his feeling is about the efficiency of pulmonary function of thoracoplasty versus resection. Doesn't he feel that, even though the thoracoplasty results are good, he sacrifices more function per case than is absolutely necessary?

DR. CHAMBERLAIN: Let me repeat the question that Dr. Mulvihill asked Dr. Semb. By doing a thoracoplasty do you destroy more function than you do by a lobectomy perhaps?

DR. SEMB: I want to stress the fact that we are not doing the ordinary thorocoplasty, but thoracoplasty with a very extensive apicolysis, and that makes it possible to reduce the resection of ribs very much, so that 95 per cent of the thoracoplasties have a resection of six ribs or less. That means that we only resect the total first rib and decreasing lengths of the next ribs. These cases, then, have no visualized deformity of the thorax, and there is very little reduction of the function of the lung.

We have examined a lot of cases of thoracoplasty so far by bronchospirometry and total function tests. About two or three months after local thoracoplasty of five ribs, there is reduction of the ventilation of 11 per cent only on that side and reduction of the oxygen consumption of 6 per cent on the same side. If we do an examination of the total function after one year, there is generally a better function totally after than before the operation. That is naturally due also to the disease which has been healed, but the loss of function by a local thoracoplasty of five or six ribs is extremely small. We have not that many figures to compile because we do not do lobectomy very often in the upper part of the lobe, but we have examined some other lobectomies and they give a bigger loss of function than the thoracoplasties.

DR. CHAMBERLAIN: Professor Semb's point, I believe, is that in the thoracic vault and the upper part of the chest where the ribs are short there is very little loss of function after his type of thoracoplasty. We had similar experience in the functional studies at Trudeau. George Wright examined twelve cases pre- and postoperatively in which we had done a modified Semb type of operation—I say modified because he wasn't doing it; I was doing it. I was trying to mimic a Semb operation, and we found 75 per cent of those patients with the five-rib thoracoplasty and the partial scapulectomy to have no significant change in function; 25 per cent had decreased function as a result of the thoracoplasty.

If I understand Dr. Semb correctly, the patient's loss of function with a selective type of operation, which is the one he does, is confined mainly to the diseased portion of lung and, therefore, does not really change the total function.

DR. WILSON: Mr. Chairman, could I ask Professor Semb if he would agree that the sixth rib posteriorly and the third rib anteriorly are probably the critical levels of function. If you exceed those levels, you lose large portions of function; and if you stay above those levels with selective collapse, your loss of function is small.

DR. SEMB: I didn't really understand.

DR. CHAMBERLAIN: The dividing line, as far as Dr. Wilson is concerned, is the fifth rib rather than the sixth rib, and a five-rib thoracoplasty is not too significant insofar as function is concerned, but as soon as you go beyond that then you begin to pay the price.

DR. SEMB: With the technique I use, I think the borderline is the sixth rib because you then resect so small a piece of the sixth rib that the scapula doesn't fall in.

DR. CHAMBERLAIN: I think there is one other aspect of this problem of thoracoplasty and lobectomy that we must consider, the most important aspect, and that is the results in these patients treated both ways.

Dr. Tuttle, could you tell us what your results, morbidity, mortality, and so forth, have been in a rather large series of patients reported last spring?

DR. TUTTLE: In that group there were almost 1,800 patients studied. They run back as far as 1947, although not many resections were done in those early years. Among the early cases there was a large clean-up problem in caring for thoracoplasty failures and patients with severe tuberculosis requiring pneumonectomy. Many of these patients had to be salvaged. We feel now that we are getting a group of patients better suited for operation.

In the entire group of patients the sputum conversion rate, that is, sputum converted according to sputum cultures or by gastric cultures, was approximately 82.8 per cent. Eight per cent of the patients were lost in the study. This is understandable in a city like Detroit because the population tends to be very flexible. In other words, when times are good, the population can increase as much as 200,000 within a few weeks' time. When times are bad, the people all go back to the hills of Tennessee and Mississippi and we don't see them any more until the plants start hiring again. There was, then, a fairly large group of lost people.

The operative mortality rate for the group for this period of almost ten years was 2.7 per cent. That, of course, has been greatly reduced. The original mortality rate was much higher than that. The total mortality rate for the group was 4.5 per cent. In other words, there was a certain group of patients who died of their disease or of other causes after the operative procedures had been done.

Our only source of comparison in this group would be with a similar series of thoracoplasty cases upon which we operated a number of years ago. At that time the group contained about 550 patients. The fatality rate in that group was higher, running about 13 per cent. The over-all mortality rate was higher and the sputum conversions as they were attested to then were tabulated at about 84 per cent.

For the thoracoplasty group a pretty crude screening type of sputum study was made. Cultural studies were not made. Sputum was examined by concentration and smear. I think that a fair number of those individuals probably would have had positive sputum on culture. I think that the over-all results in the resectional group are really much better when you take these matters into consideration.

We haven't studied our recent thoracoplasty cases. In other words, we have done no follow-up study on them.

DR. CHAMBERLAIN: Dr. Kergin, do you happen to have any figures on the work in your area?

DR. KERGIN: I am afraid I have no figures comparable to Dr. Tuttle's. I have a few figures that may be contributory, though. In the period from 1943 to 1952 at Toronto Hospital for Tuberculosis, we did 1,114 thoracoplasty stages on 615 patients, with 7 postoperative deaths: a stage mortality of 0.61 and a patient mortality of 1.14 per cent. At that time our figures reported an 85 per cent conversion rate.

In the year 1951 we still did a lot of thoracoplasties. With the help of chemotherapy we reported 82 patients that year who had had thoracoplasties, with no deaths and a 97.5 per cent conversion rate. That means nothing. That was a very short follow-up.

A figure that I do have, however, has to do with relapse. Yesterday there was a good deal of discussion about relapse, and I got a little confused. To me a patient who in the course of treatment or under drugs shows an exacerbation of the disease is a failure of treatment, not a relapse. By relapse I mean a patient who has completed the treatment advised by his physician and then shows a recurrence or recrudescence of the disease.

Over the period from January, 1953, to January, 1958, the Toronto Hospital for Tuberculosis discharged some 1,500 patients who had medical therapy only without surgery, and they

showed a 3 per cent relapse rate judged by ordinary follow-up in the clinic: clinical assessment, cultures of sputum and gastric washings, and repeated X-rays.

In the same period of time, 341 patients were treated surgically and 3 patients had relapses, a 1 per cent relapse rate. Among these patients the shortest follow-up is less than a year, the longest a little more than five years.

DR. CHAMBERLAIN: Did I not hear your figures on mortality rate in your resection cases?

DR. KERGIN: I didn't give you those. I can. Our excisional cases in the 341 patients operated on in that period of time consisted of 30 pneumonectomies, with 3 deaths, a 10 per cent mortality; 95 lobectomies, with 3 deaths, a 3 per cent mortality. Two of those deaths followed the second lobectomy on the second side. Only one patient died from a primary lobectomy. Then there were 28 cases of lobectomy plus segmental resection, no deaths; 154 cases of segmental resection, with one death, 0.7 per cent mortality; 34 cases of wedge excision, single or multiple, no deaths. The total figures are 341 excisional operations, with 7 deaths, a 2 per cent rate.

DR. CHAMBERLAIN: We had Mr. Edwards' figure of his mortality as 1.7 per cent. Is that right, Mr. Edwards?

MR. EDWARDS: Yes, that is right.

DR. CHAMBERLAIN: To be exact, 1.71 per cent. And there was an 87 per cent conversion in Mr. Edwards' cases.

Now, could you tell us, Dr. Wilson, about your results in resection and thoracoplasty?

DR. NORMAN WILSON: First of all, I would like to make a point that they are not comparable, and they are not comparable for anybody else sitting up here probably except for Professor Semb because we are doing thoracoplasties for lesions we are afraid to resect. It doesn't make any sense to take a whole group of serious resistant cases and start comparing results with a series of cases in which predominantly you are taking out closed lesions. I would like to make that point, that this in my mind is not a comparable statistic.

If I may, I would like to present what I think is representative of what can be done even with bad cases in the chemotherapy era with thoracoplasties. At Rhode Island State Sanatorium in the years 1952 to 1954, we had 107 consecutive cases in which, except for three or four cases, there was no combination of a closed cavity and a negative sputum (between 70 and 80 per cent of these people had positive sputum and most of them had positive sputum because they had had irregular drug therapy, not the fault of the institution always, but because the patient signed out or had treatment elsewhere, and so forth). Eighty-seven per cent of those people had lesions controlled by thoracoplasty alone. Eleven of the 14 failures were eventually salvaged by resection or chemotherapy or both. We followed them up one to four years later: one patient was dead, 94 per cent were completely well, and one had had an exacerbation on the side of operation

I think that is a little different concept than has been given here about thoracoplasty. I still think that, if you have a good, clean resection, it is the operation of preference; but I myself have never been able to take the serious case and operate on it with anything like this mortality or morbidity rate. In my own hands, if I shifted over to resection in the resistant case or the advanced case, I would be doing an unnecessarily serious operation on a lot of perople that can get well with a simple procedure.

The results, as you know, from the cases that we presented are very similar to these, showing the eventual control of the ipsilateral lesion at about 95 per cent. More of those required resection. In the follow-up, only 5 people had died: 3 of coronary occlusion, one of metastatic cancer, and one of an unknown type of acute anuria, causing death twenty-four hours after admission to the hospital.

In neither of these series was there a postoperative death. With resection last year in our clinic we were getting more and more very longstanding drug-resistant cases to treat all the time. Our mortality rate with pneumonectomy last year in cases unsuited for thoracoplasty was 18 per cent. I think anyone who is attacking this kind of case will have similar death rates.

I believe, if I remember correctly, Dr. Tucker, in the Veterans Administration it was something like 14 per cent in that type of case. I think results are determined by the material at hand. I think resectional statistics are completely confused by a whole host of closed lesions. I keep telling my residents that if I had a fourth-year

high school student with two clamps and two stitches he might do part of them without any trouble.

DR. CHAMBERLAIN: Dr. Raleigh, can you give us the figures at Sunmount?

DR. RALEIGH: I don't have the details with me, Dr. Chamberlain. I can just tell you what I recall. Just last summer Dr. Victor Kimmel, who, I believe, is here in Philadelphia, summarized our results from 1950 through 1957. In 807 consecutive resections for tuberculosis the operative mortality (and that included deaths up to three months postoperatively) was 0.75 per cent. This ranged from about 5 per cent in pneumonectomies to about 0.4 per cent in segmental and subsegmental resections.

The incidence of successful results was about 85 or 86 per cent. Among the unsuccessful results were those patients who failed to close cavity and convert sputum and those who after an initial good result subsequently suffered relapse.

One of the interesting things that Dr. Kimmel pointed out or that he analyzed was the significance of the single positive culture that we sometimes see postoperatively. He took a series of patients (I think there were sixty) in whom the first sign of a reactivation or an apparent reactivation was a single positive culture followed by a series of four to six negative cultures. In other words, that is what made it single. The subsequent follow-up of these sixty cases showed that about 25 per cent of the patients later developed definite tuberculous relapse with either further positive cultures or further positive cultures and unfavorable X-ray change, frequently the development of cavity. Seventy-five per cent of these patients with initially single positive cultures had no further evidence of reactivation.

I think what Dr. Wilson said is quite true. The surgical statistics are certainly conditioned by the type of material you operate on, but I think in this series that Dr. Kimmel reports that about 65 or 70 per cent at least were cavitary anyway.

DR. TUTTLE: I just wanted to say one other thing concerning these statistics. I agree with Norman Wilson that they aren't comparable. At least your thoracoplasty groups, many of whom were reported many years ago, are not comparable with the present resectional group.

Most of the large series of resection cases date back a number of years when certainly surgeons were not as adept at doing this type of work as they are now. Last year among three or four hundred pulmonary resections at Herman Kiefer Hospital there was a 1.2 per cent operative fatality rate up to three months after operation. Furthermore, any patients who died of bronchial fistulas at a later date were included among the postoperative deaths.

Then, too, these figures are not altogether accurate because a lot depends on who is doing the operation. In many of the large institutions many of these operative procedures are done by members of the resident staff under supervision. Naturally, in instances like that, the fatality rate is going to be higher than when the operation is done by people with perhaps more experience.

We have one small sanatorium in which we have been operating for a good many years and in which we have done pretty nearly a total of five hundred surgical procedures, all of which have been done by Dr. Day or myself. In those five hundred cases there have been no deaths. So it makes a lot of difference, not that we are better than the residents, but at least we have been around longer.

All of those things have to be considered, so I don't think we can depend, as Dr. Wilson said, too much on just what your fatality rate is.

DR. CHAMBERLAIN: Now, Professor Semb, tell us what your follow-up figures are and also what your results are from your large series of thoracoplasties and resections.

DR. SEMB: To enable you to understand my figures, I would like to say a few words about the indication. After chemotherapy was introduced I found that there should be a combination of both thoracoplasty and resection, that both of them have their own field of application; and to try to find out, I have made a surgical experiment now for over ten years. I always followed the same indications to find out the place for thoracoplasty and the place for resection.

I did it in the following way. In the upper and posterior part of the lung (that means the upper lobe and the apical section of the lower lobe) I always used apical thoracoplasty with apicolysis regardless of whether the lesions were sclerotic or not, even in a patient with a totally destroyed upper lobe. I only excepted the solitary tuberculomas.

In the next location, the lower and anterior part of the lung, in which thoracoplasty does not give a selective collapse, I used resection as the main treatment. In addition I had to do a lot of resection in patients, especially from other hospitals, with residual cavities after thoracoplasty.

The third location is the lesion in the whole lung. When the patient had cavities scattered in the whole lung, without stenosis of the main bronchus, I did a six- to eight-rib thoracoplasty in order to save a part of the lung for function; this is possible in these cases. With a totally destroyed lung I naturally did a total thoracoplasty and later, if necessary, resection. I have found it a great advantage to do a thoracoplasty first. Then the resection is much easier to do, if necessary. It is necessary in 40 to 50 per cent of the cases. You can do it practically without danger of bronchopleural fistula. We had only one fistula in forty cases.

The material in our series was around 1,100 cases in the years 1949 to 1954, with four years' observation afterwards. The preoperative treatment was not less effective than we have today. There were many advanced cases because you had to take into consideration patients who were previously regarded as inoperable. The postoperative treatment was a little ineffective according to our present knowledge, and relatively short.

The follow-up study of these patients is made by the Public Health Service. The sputum control is made with guinea pig inoculations. There is in addition clinical and roentgenographic study.

The thoracoplasty group consisted of 817 cases. Among these, 5 per cent of the patients have had bilateral operations. These patients have been followed-up from four to nine years. There has been an immediate postoperative mortality rate of 1.5 per cent. Eighty-eight per cent are now fully restored to health without demonstrable tubercle bacilli. In addition, 2 per cent of the patients who had apparently recovered from their tuberculosis died of other causes. This means that practically 90 per cent were apparently cured. The late deaths totaled 6.3 per cent.

During the years from 1949 to 1957 we carried out bilateral thoracoplasty in 88 cases. This is our most common procedure in cases of bilateral disease. The postoperative mortality rate was 3.4 per cent. There were 11 per cent late deaths. In 82.9 per cent of the cases, recovery, according to the standard mentioned, was attained.

There were 313 resection cases in the whole series. The operative mortality rate was 3.2 per cent. The late death rate was 8.9 per cent. The recovery rate was 78 per cent according to the described standards.

There are in all 1,100 cases in this so-called surgical experiment, with four to nine years of follow-up observation. The combined operative mortality rate was 1.9 per cent. In 85 per cent, recovery according to the described standards was attained. Tubercle bacilli are still demonstrable in 2.6 per cent of the patients. The late mortality rate was 7.8 per cent.

DR. CHAMBERLAIN: And I saw his notes which said "unknown, 2 per cent." The follow-up is excellent in Norway.

We only have a few moments more. If the audience has any questions, I would like to ask that you have them ready. While you are thinking of these questions for the members of the panel, I would just quickly like to poll the panel on one question: Will you operate on patients who have resistant organisms and what operation do you prefer?

Mr. Edwards?

MR. EDWARDS: Yes, we operate upon these because the physician appears to be helpless. So far we have done resections, but possibly with the occasional case we might go over to the side of the thoracoplasty because we are not quite sure just how these cases are going on. But we cover them with the secondary drugs when we do, such as viomycin, cycloserine, and others.

DR. CHAMBERLAIN: Dr. Tuttle?

DR. TUTTLE: I think I had a favorable answer to that before. We don't let the so-called resistant-organism–patient influence our thinking as far as the procedure is concerned. In other words, if it is a patient whose case is suitable for resection, then resection is done. If it is one who is better treated under any circumstances by thoracoplasty, that is the procedure which we follow.

DR. CHAMBERLAIN: Dr. D'Esopo, how do you feel about it?

DR. D'ESOPO: They are operated on in West Haven. I think we are doing fewer thoracoplasties in these individuals as we have more secondary

drugs to cover resections, especially cycloserine and pyrazinamide.

DR. CHAMBERLAIN: Dr. Kergin?

DR. KERGIN: We carry on very much as if the organisms were susceptible and we use pyrazinamide with some gratifying effect. The only qualification I would make is that, if we have a patient about whom we are in a little doubt as to whether thoracoplasty is a better procedure than an excision, the presence of resistant organisms might "shade us" to thoracoplasty. Aside from that qualification we carry on the treatment otherwise used in a patient with sureceptible organisms.

DR. CHAMBERLAIN: Dr. Davidson?

DR. DAVIDSON: I don't think this question can be as easily answered as "do you prefer stuffed olives to ripe olives?" I think the question of the character, extent, and location of the disease, the age of the patient, how he has reacted previously, all have to be considered. I would say, as I indicated before (contrary to what Dr. Tuttle has stated) that I don't think the surgeon is fearful, but he is fearful for the patient. That is a distinction. We feel that in resistant cases, and our feeling in that direction is growing, the patient should have thoracoplasty.

Mr. Chairman, with your permission I would like to take one minute more in regard to what I think is a very important problem: the so-called open-healed cavity. And by the open-healed cavity I mean the cavity in the patient who has received isoniazid, who has an exquisitely thin pencil-lined cavity wall, and has been "negative" for one year.

At Sea View Hospital the late Dr. Cherkoff, who died four months ago (and this began about five and a half years ago) tried to impress upon us the advisability and necessity for not operating upon these patients. I have not been able to get the exact statistics, but I am certain I am very close to them.

In the clinic there are now 24 patients with open-healed cavities who have not been operated on. One case has gone on for four and a half years, many between three and four years; the majority, however, less than that. Not one patient has had a positive sputum, hemorrhage, infection, or any disability. I merely asked you for this opportunity to present this because I think it is a very important point.

DR. CHAMBERLAIN: It is an important point. It is one of the points Mr. Edwards outlined for us that I didn't get to, unfortunately. We wanted to talk about the open-healed cavity and we also wanted to talk about space problems, but we just couldn't crowd it all in.

Could you answer that one question, Dr. Wilson, about operating on patients with resistant organisms?

DR. NORMAN WILSON: Under these circumstances, in which, in my opinion, the risk of resection goes up by 10 per cent, we shift to thoracoplasty and resect the failures.

DR. CHAMBERLAIN: How do you feel about it, Dr. Raleigh?

DR. RALEIGH: I think in a patient who is otherwise eligible for resection and who has the disadvantage of resistant organisms, we go ahead and resect, tending to veer away from segmentals and subsegmentals; preferring either at the expense of additional lung tissue, if necessary, to do an anatomic resection, such as a lobe. Of course, we do use whatever secondary drugs are available.

DR. CHAMBERLAIN: I think I might add that, if there is a clean-cut indication for resection, as Dr. Tuttle pointed out, we go ahead with the recommendation for resection if we are not leaving behind actively diseased tissue even if resistant organisms are present.

Is there anyone in the audience who would like to ask a question of the panel? Is there anyone in the accessory panel who would like to ask a question?

Dr. Muschenheim, you have been awfully quiet. Is there any one apsect of the discussion this morning that you would like to comment on?

DR. MUSCHENHEIM: I do think that one aspect which came out very clearly was this question of the increasing importance of the drug-resistant cases, and I think that from the standpoint of the internist one could make the observation that we are going to be asking surgical help more and more for just this type of case, as our indications shrink somewhat for surgical help in tuberculosis.

I think it was commented on by several of the panel that fewer closed lesions are being resected. Dr. Davidson has pointed out the fact that one possibly can select some of those cases of open negativity which really represent true open-

healing, so that there will be an increasing residue of patients not only with persistently positive sputum, but with persistently positive sputum with resistant organisms.

As I see it, this will be the problem of the future and, much as we would like to avoid presenting you with these more difficult problems, I think these are the ones that we are going to have to have your help with.

DR. CHAMBERLAIN: May I take this moment, then, to thank the panelists, the audience, and the accessory panelists who made their contributions today.

The meeting is adjourned.

PANEL SIX

Panel members, left to right: William B. Tucker, Philip D'Arcy Hart, James E. Perkins, David A. Cooper, Johannes Holm, Georges Canetti, Julius L. Wilson.

PANEL SIX

THE FUTURE PROBLEM OF TUBERCULOSIS: PROGRAM FOR ITS CONTROL

Chairman: DAVID A. COOPER
Introducer: JOHANNES HOLM
Panelists: GEORGES CANETTI
PHILIP D'ARCY HART
JAMES E. PERKINS
WILLIAM B. TUCKER
JULIUS LANE WILSON

DR. COOPER: It is my pleasure to call to order this sixth and final panel in this symposium: The Future Problem of Tuberculosis: Program for Its Control.

I would like to introduce our panel, all of whom have been introduced to you before:

Dr. Johannes Holm, Chief, Tuberculosis Section, World Health Organization, Geneva.

Dr. Georges Canetti, Chief of Laboratories, Institut Pasteur, Paris, France.

Dr. Julius Lane Wilson, Director of the Henry Phipps Institute in Philadelphia and Director of Medical Education of the American Trudeau Society.

Dr. James E. Perkins, Managing Director of the National Tuberculosis Association.

Dr. Philip D'Arcy Hart, Director, Tuberculosis Research Unit, Medical Research Council, London.

Dr. William B. Tucker, in charge of the Pulmonary Disease Section of the Veterans Administration.

Dr. David A. Cooper is Professor of Medicine, School of Medicine; and Professor of Clinical Medicine, Graduate School of Medicine, University of Pennsylvania; Chief, Department of Medicine, Philadelphia General Hospital; Physician, University of Pennsylvania and Pennsylvania Hospitals, Philadelphia.

DR. COOPER: I mentioned where these various panelists are from, but they warned me at luncheon today that they were speaking as individuals and not as representatives of the various places from which they came. I forget the usual statement that is on the bottom of all publications from the Veterans Administration, but they assume no responsibility. This is a personal matter all the way through.

In beginning our panel, our introducer, Dr. Holm, has promised to outline our problem and then we will have a general discussion.

DR. HOLM: I have interpreted the title given to this panel discussion as meaning: How do we visualize the tuberculosis program during the next ten years, and what problems do we anticipate in the planning and execution of this program?

As you have asked a representative of the WHO to introduce this subject for discussion, I take it that you wish to have the problem considered from a global point of view, which we have to adopt in WHO, rather than from the point of view of any one country.

During the first five panel discussions, several of the specific measures which must form part of the tuberculosis program have been discussed in considerable detail. The discussion today should concentrate more on the tuberculosis program as a whole, including, perhaps, some detailed consideration of those measures which have not been fully discussed before.

I am going to discuss the problems of the future tuberculosis program from the point of view of the public health administrator. One reason is that I am convinced that the tuberculosis program in the future will have to be planned much more on the community approach, many of the measures being applied on a community-wide scale. For the planning and direction, then, of the future tuberculosis program we will need not so much a clinical tuberculosis specialist, but a public health specialist experienced in the control of communicable disease.

There are certain questions which a public health administrator responsible for planning the control program for any communicable disease must consider, and I propose that we use today in the discussion these headings for individual subjects. These three subjects are:

1. What should be the objective of our program? In other words, what are we aiming at?

2. What is the extent of the problem and how can we measure it? And a problem closely related is: How can we evaluate the effect of our program?

3. This is really a group of questions: What measures are at our disposal that will be effective in reducing the incidence and the prevalence of the disease? How effective are they, and how can they be applied in a practical way?

Reliable and practical answers to these questions must be obtained before we can start planning the program. Also, to draw up a realistic plan we need to know what resources in terms of funds, equipment, and personnel are available or can be mobilized for the program. However, the resources vary with the country, and we may, accordingly, group the countries into those which are technically and economically less developed and those which are more, or even highly, developed.

I propose that for the purpose of the discussion today we leave aside the problem of financial resources, equipment, and personnel, assuming that these will be available as required. You will realize that this means that we will limit our discussion to the future tuberculosis program in the more developed countries.

I see it as my task today to present for discussion each of the questions which I have mentioned, without at this stage trying to treat them fully or trying to answer them. Only in order to stimulate discussion, I will venture to suggest some answers and also to make some statements which some of you might consider provocative.

Let me come to the first question: our objective. From the discussion at lunch there is no doubt what I consider our final objective. The final objective must be the elimination of tuberculosis as a world problem, the complete eradication of tuberculosis, I should say. But I consider it important that, besides this ultimate objective, we try to define more immediate objectives, because our program must be developed by certain stages. Therefore, I would propose as an immediate objective for our future tuberculosis program the elimination of tuberculosis as a public health problem. I will have to define a little what I mean by this.

I mean thereby that we are aiming at reaching the stage at which a specific tuberculosis program is no longer necessary, the incidence of tuberculosis having been so much reduced that it can be left to the general medical and public health facilities of the country to take the necessary action for the few cases of tuberculosis that we can still expect will arise in a number of years.

This stage can be arrived at after the first part has been reached, in WHO terms, the "surveillance stage." And this last stage should then ultimately lead to the eradication of tuberculosis.

It is important that we define in precise and objective terms the point at which tuberculosis ceases to be a major public health problem, a point which I propose might be termed the "target point" of our elimination program. In WHO we consider that this target point has been reached when no more than 1 per cent of the children in a community are spontaneous reactors to tuberculin at fourteen years of age, the WHO standard method for tuberculin testing being used. To my knowledge, this target point has not yet been reached in any country. It has been reached in some parts of a country, but not for any country as a whole.

The second problem is: How do we measure the extent of the tuberculosis problem? The extent of the tuberculosis problem in a given country has up to now been measured by the tuberculosis mortality and morbidity rates. I think we all agree that with the present highly effective treatment of tuberculosis, which has reduced the case fatality ratio to a fraction of what it used to be, tuberculosis mortality is no longer of any use for measuring the extent of the tuberculosis problem in a country.

Even tuberculosis morbidity, usually expressed as the number of newly reported cases of tuberculosis per 100,000 population, is of limited value for several reasons. First of all, the number of newly reported cases of tuberculosis depends upon the intensity of the case-finding efforts made in the community; and much interpretation, therefore, is needed before the morbidity figures can be used as an index of the tuberculosis problem.

Furthermore, as there is no universally accepted standard for what is to be considered a notifiable case, and as the standards that are used vary according to place and also according to time, it is evident that, even in the countries with the most reliable health statistics, the tuberculosis morbidity figures are of little value.

In WHO we have devoted much effort to developing well-standardized methods for prevalence surveys for tuberculosis. These surveys involve examination for tuberculosis of randomly selected sample groups. Data are collected on tuberculin skin sensitivity, on chest X-ray pathol-

ogy, and on the presence of tubercle bacilli in sputum samples, well-standardized methods and techniques being used throughout. Such prevalence surveys have been carried out in a number of countries and have proved a most useful means of obtaining precise and comparable indices of the extent of the tuberculosis problem.

When we approach the target point of our elimination program, prevalence surveys become impractical because the population groups that have to be examined in order to arrive at reliable estimates of the prevalence of infectious tuberculosis will become too large. But at that stage, use can be made of the tuberculin test alone.

In this connection I should like to stress the need for uniform methods for tuberculin testing and for carefully standardized tuberculins. This, in my opinion, is a condition for using the tuberculin test for prevalence surveys for tuberculous infection, but a condition which is not fulfilled in a number of countries.

Such surveys carried out on randomly selected samples of the total child population at age fourteen will give us an indication of how close we are to the target point as I have defined it.

Then the third group of questions: The measures on which we have to rely in our future tuberculosis program fall into two different groups: BCG vaccination and application of the antituberculosis drugs.

BCG vaccination has not yet been discussed thoroughly during this meeting. In WHO we have no doubts about the protective effect of a correctly applied BCG vaccination. In the controlled trial carried out by the British Medical Research Council, vaccination with a good standard vaccine was found to be about 80 per cent effective; that is to say, the incidence of tuberculosis among the vaccinated subjects amounted to about one-fifth of that among the controls.

The results recently published of the controlled trials undertaken in the United States of America have not altered our views concerning the protective effect of BCG vaccine. They have, however, confirmed that for the vaccination to be effective a potent vaccine must be used and a strong and stable tuberculin sensitivity must be induced.

From data collected in field studies in different parts of the world, we know that it is possible to induce the necessary high degree of tuberculin sensitivity.

In my opinion, BCG vaccination should have a definite place in the future tuberculosis program in most countries. Even when the goal of the elimination program is within reach, the adult population should be kept tuberculin positive and the children should, therefore, be vaccinated before leaving school.

The use of antituberculosis drugs has already been discussed during these panel discussions in considerable detail. What we should discuss today is the place of these drugs in the practical program.

All definite, bacteriologically positive cases of tuberculosis or, as I would prefer to put it, all sources of tuberculous infection, should receive chemotherapy. Such true chemotherapy should give rise to relatively few problems, considerable experience having been gained in this field.

In addition, the antituberculosis drugs should be used for prophylactic treatment of potential sources of infection. Provided the drug or combination of drugs used can be self-administered at home with little inconvenience, it would seem justifiable or even advisable to treat prophylactically the so-called "high-risk" groups, those who show roentgenographic changes found to be correlated with a high risk of developing bacillary tuberculosis.

One of our problems in the future program is how to define the "high-risk" groups. For this purpose epidemiologic studies are needed, involving long-term follow-up of large population groups with low exposure to tubercle bacilli. One such study is being carried out in Denmark under the so-called Danish Tuberculosis Index.

At the present stage of our knowledge, I would consider it justified to give prophylactic drug treatment to every person with definite pulmonary X-ray pathology which permits of no obvious diagnosis other than pulmonary tuberculosis. This is the type of case which used to be kept under observation for some time by the tuberculosis dispensaries. Simple supervision of these cases should now be replaced by prophylactic chemotherapy, especially the administration of isoniazid combined, of course, with follow-up examinations.

With regard to true prophylaxis, the administration of drugs to persons with no signs or symptoms of tuberculosis except positive tuberculin reactions, our experience is at present very limited. Therefore, more evidence of its effectiveness will be required before mass prophylaxis can be included in our tuberculosis program.

There is, of course, one exception which also came out clearly in the discussion in the first panel, that is, that antituberculosis drugs should be given to recent converters to the tuberculin test. Now the question is whether that should be considered really prophylactic treatment or true prophylaxis.

One of the big problems with which we are faced in planning the future tuberculosis program is how to find the persons to whom we should give antituberculosis drugs. If our program is to be effective, a high proportion of all those in a community who require chemotherapy or prophylactic chemotherapy must be discovered; most of the actual and potential sources of infection must be traced. For this purpose the existing system of tuberculosis dispensaries is inadequate, since the main function of the dispensaries is to carry out specialist examination of people referred because of symptoms of tuberculosis, and a high proportion of the persons in whom we are interested have no symptoms at all.

Community screening for tuberculosis is essential, and the examinations should be organized in such a way that they are acceptable to the population, cause the least possible interference with the daily life of the people, and at the same time ensure that a high proportion, close to 100 per cent, of the population (especially of the oldest part of the population) is actually reached. Studies are needed, in my opinion, to determine the best way of organizing community screening, and for this purpose the assistance of sociologists will be essential.

I should like to emphasize that I am not in any way suggesting that tuberculosis dispensaries are no longer necessary. During the elimination stage they are needed for the follow-up examination of people under treatment and, when we reach the surveillance phase of our program, the tuberculosis dispensaries, having been transformed by then into chest clinics, will have an important part to play.

The last important question which I should like to ask, and to which it is very important to have an answer, is how to ensure that the persons selected for domiciliary treatment will self-administer the drugs regularly and for a period as long as one year. It is not, of course, enough just to hand the drugs to those requiring treatment or prophylactic treatment. Steps must also be taken to ensure that they are taking the drugs regularly and for the necessary period of time.

This is partly a matter of health education, but some sociologic and psychologic problems are involved which can only be solved by means of well-planned studies. This whole complex of problems is usually referred to as the acceptability of long-term drug treatment.

Now, Mr. Chairman, I hope that these introductory remarks can serve as the basis for the discussion. I am quite aware that I have raised several problems so that not all could be taken up at once, but it could be that they could be taken up one by one.

DR. COOPER: Dr. Holm, you certainly have presented us with a number of interesting questions on which I shall enjoy the comments of my high-powered panel.

First, maybe I should ask Dr. Perkins as to the objectives, as I think you posed your questions, but I prefer to change the schedule a bit and would like to ask Dr. Canetti if he would give us his thoughts on what the objectives of our program should be.

Dr. Canetti, from the standpoint of a pure research worker, what do you think we ought to plan with respect to the over-all program, our objectives, and the implications from the viewpoint of a research scientist.

DR. CANETTI: I think as to the ultimate objective, of course, there is no doubt that it should be eradication. This is obvious and we all agree on that; but I think we want to come to statements for shorter periods of time, for instance, what should be done immediately as a sort of general policy.

I think our general policy should be to work out methods which can be applied under all conditions in the world, even under the worst. This seems to me extremely important. We have now lots of methods of treatment, of prophylaxis, and we have really a choice among these methods; but, as I said earlier at the luncheon meeting, what we do not take into consideration sufficiently is whether these methods can be applied under conditions which are very different from those existing in our countries.

I think that our major goal for the immediate future should be to work out methods which can be applied under all existing conditions, even if we in our countries stick to still more refined methods. This should be the goal for case finding as well as for treatment and prophylaxis.

DR. COOPER: I think after that we can ask

Dr. Perkins to repeat himself and give us his comment on the objectives of our program.

DR. PERKINS: I shall not repeat myself, I assure you, but I would like to comment on Dr. Holm's proposal that our target point be to eliminate tuberculosis as a public health program. I know what you are trying to do, Dr. Holm, and I agree with the principle. In other words, eradication is perhaps so far in the distance and so nebulous that you want to have a target point which is closer for us to "shoot at"; this, I think, is a very good idea.

What I object to, I think, is perhaps your saying that up to that target point it is a public health problem, and from that point on you don't call it a public health problem any more. I think that can be resolved rather simply if you will agree with me by changing this to the statement that the immediate objective of the tuberculosis program must be to eliminate tuberculosis as a critical public health problem, and it will still be a public health problem beyond that point. At least I feel that smallpox, diphtheria, influenza, and so on, which do not have special programs at the present time, are still public health problems.

Would you accept that modification?

DR. HOLM: Completely.

DR. COOPER: Thank you very much, Dr. Perkins.

Dr. Tucker, who is intimately tied in with this thing from a federal viewpoint, what are your thoughts on the objectives at the present time?

DR. TUCKER: Dr. Cooper, because of the unfortunate connotations of ten-year plans or five-year plans, I therefore would not propose that we think in such terms. I merely agree in principle entirely with Dr. Holm and with the modification of the proposal that Dr. Perkins has proproposed which has been accepted by Dr. Holm. It occurs to me that we already have the techniques at our command without any major new developments for achieving this goal of eliminating tuberculosis as a critical public health problem. The problem is clearly the application of these control measures. It is perfectly obvious that here we are dealing with human beings and, to the extent that we do not have complete control of human beings, sociologically, politically, and in other ways, this creates the difficulties.

It has been clearly demonstrated that the same principles of control of tuberculous infection in nonhuman animals can be achieved very readily, so we need to consider these factors as well.

DR. COOPER: Thank you very much, and I will call on Dr. Hart, who will give us his views on this part of the question.

DR. D'ARCY HART: Mr. Chairman, I want to be sure that I am not going on to the next two questions in what I am going to say. Will you check me if you find that I am?

To me in Britain it seems rather idealistic even now to talk about eradication and, as the Medical Research Council is much concerned not only with Britain but with other parts of the Commonwealth, much of which, as Dr. Canetti has pointed out, are underdeveloped in health, I cannot help but feel biased in favor of considering that as well. It will be a long time before eradication will be achieved, and I would like to mention two possible obstructions on the path. I think we shouldn't get the idea that we are just going to "free-wheel down the hill" with the same methods, whatever they may be, until we get to the eradication corner.

I see two dangers. First of all, in the better-off countries there has been very little—or perhaps nobody here feels it is a danger at all—but are we quite happy with the amount of drug resistance that is being built up en masse? Sitting here one got the idea that it was an outrageous thing to get drug resistance in the course of treatment, but I feel sure that many clinicians do find drug resistance either because they aren't perfectionists in treatment or because they are by mistake treating patients that already are slightly resistant. I feel that a lot of clinicians get patients whose infections are already drug resistant. In the course of time, are we quite happy that we are not building up a problem? We feel that we may well be doing so in Europe, anyway. That is one thing.

The other thing is this, and I should like to bring us right down to a country like India and to show how different, as Dr. Canetti said, are the considerations. Recently when the Indian government invited the World Health Organization to assist it, and the WHO very nicely asked the British Medical Research Council to carry out the work, the problem was proposed in a way which I think will be quite unfamiliar to those who are restricted to the favorable countries.

Their problem was this: We have an enormous tuberculosis problem. Our main effort is to try

and reduce the infectors. We are not so concerned with the benefit of treatment to individuals. What we are concerned with is whether we can introduce some form of mass treatment which will reduce our pool of infectors so that, in its turn, a beneficent spiral will be created so that we reduce the number of new cases.

In other words, can mass treatment produce prevention? That is a different point of view: not, will mass treatment benefit those people primarily who are ill now; but, will it in the future create a situation in which there will be less chance of new cases. Contrariwise, can we be quite sure that, with the more advanced methods of treatment, if they are carried out ineffectively or with the wrong drugs, we shall not be increasing the number of cases by prolonging lives and even increasing the pool of infection?

That is the sort of public health approach in a country like India. It is really utterly different, and there is the great problem that has to be overcome before we start any form of travel down the road toward eradication.

DR. COOPER: Dr. Wilson, we have left you alone for a while.

DR. WILSON: I certainly agree fully with Dr. Hart in feeling that even this ten years wouldn't accomplish a great deal, and that eradication certainly must be a very distant goal whatever way we reason it. If we think of bovine tuberculosis control in the United States, for instance, started in 1917 or thereabouts (I believe Michigan was one of the first states certified as having less than 1 per cent or a fraction of a per cent of cattle reacting to tuberculin), it was found necessary to spend large sums of money testing cattle and slaughtering the reactors since then; but a slight economy in the War years or at the end of the War resulted in a marked increase in bovine tuberculosis in Michigan until about 1955; so now they have to spend twice as much money. I think, then, that the objective of eradication, if there is any analogy between bovine tuberculosis and human tuberculosis, must be very remote.

I would also like to point out that we have some charts at the Phipps Institute that Dr. Flick drew up in 1882 when writing a paper on tuberculosis in Philadelphia. He charted the phthisis in the Fifth Ward for the years 1865 to 1880. Incidentally, he threw in a few maps of that ward that showed scarlet fever and one that showed smallpox, and at the end of the 1870's, mind you, some eighty years after Jenner introduced a really effective vaccine, the deaths from smallpox in that ward in Philadelphia were a considerable number. I just throw this thought out as a caution to overoptimism.

DR. COOPER: Dr. Perkins wishes to make another comment.

DR. PERKINS: I think we all agree that total eradication is a long way off, and I think that is the precise reason why Dr. Holm gave us an intermediate target to shoot at. I would like to comment on that. He said that this intermediate target is to have no more than 1 per cent of children of fourteen years of age as spontaneous reactors to tuberculin. I am perfectly willing to accept this target. We have to have something, and I think that is probably as good as anything.

The only thing that worries me about this is that I gather, Dr. Holm, you thought at that time you could then discontinue any special program, that it would just be the usual surveillance by the health department from that point on. But I wonder how many reactors in the older age groups we would have even when we reached the point where only 1 per cent of the fourteen-year-old children reacted. It seems to me there still might be a pretty substantial group of reactors in the older ages who will breaking down with tuberculosis; and assuming now that these studies as to the value of isoniazid to such reactors in the older ages who will "break down" with tuberculosis, and assuming that these studies on the value of isoniazid to such reactors in preventing such breakdown actually pan out, and we want to use isoniazid, it seems to me we might at that point still find it necessary to preserve a special program, special personnel, and so on, to concentrate on that older reservoir of reactors.

DR. COOPER: Dr. Holm would like to comment.

DR. HOLM: Dr. Perkins has mentioned exactly the very difficult problem we are up against in speaking about eradication. The difficulty in speaking about tuberculosis eradication is the persistence of the tubercle bacilli in the tuberculin-positive reactors and there the difficulty is much greater than in malaria. In malaria it is known that the organisms do not usually persist more than three years, so that the surveillance period can be limited to three years. If there is no new case of malaria in an area in three years, then it can be considered that an individual is sterilized for the parasite.

In tuberculosis it is quite different, but it is

just one of the unknown problems. We do not know how many of the positive reactors who have tuberculin reactions for many years do actually develop tuberculosis. There is one study that I should like to mention in this connection. In Denmark we had plenty of bovine tuberculosis until just after the War. It was eradicated in a relatively short time, and finally the country declared bovine tuberculosis eradicated in 1950.

At that time I think we could estimate that half of the population had been infected with bovine tubercle bacilli. In the following year new cases of pulmonary tuberculosis caused by bovine tubercle bacilli were found in adults, but the number is decreasing year by year so that now after eight years there are only a very few cases. It might be, then, that we don't have to wait a whole generation, but it is exactly because of this period when we don't have really many cases of pulmonary tuberculosis, not many sources of infection, that we have the reactors. But I am speaking about the surveillance states in which we do not need all of the same active measures as we had during the period when we had to hunt for the sources of infection.

Dr. Cooper: I was glad to hear Dr. Wilson refer to bovine tuberculosis. Unfortunately, we can't apply the same principles of treatment; we can't slaughter human beings to eliminate it; and since it has taken that long to handle bovine tuberculosis, we can anticipate a longer time with human tuberculosis.

I think with that we can move on to the next question: What is the extent of the problem and how can it be measured? I think we will start off with the first part of that. Of course, that question can be broken up into several parts, such as the mortality rates, the morbidity rates, and the infection rates, such as the positive tuberculin reaction. I think perhaps we will start with Dr. Hart.

Would you comment on the first part of that question; as a means of measuring the extent of the problem, discuss first the mortality and the morbidity rates. I guess you had better take mortality to start with.

Dr. D'Arcy Hart: I think I would certainly agree that mortality rates are of quickly diminishing value except as a purely factual bit of information, and I will pass on to morbidity. I wouldn't entirely agree with Dr. Holm in dismissing morbidity, though I think he was thinking of it from the international standpoint and, from the international standpoint, probably it is a poor method and always has been a poor method of comparison.

I don't suppose he would, on the contrary, disagree with me that within a country morbidity rates, meaning notification rates, where there is notification, are useful. In Britain we are well aware of the artificial factors, such as changes in intensity of finding, case finding, for example, as introduced by mass roentgenography, and so on. We feel that some of those factors have stabilized themselves, particularly mass roentgenography, and that the notification rates are of some use.

Certainly that is the only form really of changing statistics that we have short of the *ad hoc* prevalence surveys which we are going to discuss. These come in and can be used. Recently we made a plea in Britain that the published figures should have much narrower age groups. At present they are very wide and really not of very much use. For example, one would like to know the prevalence in certain divisions of adolescence which aren't specified at present; and they are being provided.

With that sort of information one can make epidemiologic analysis, and it is being done in a certain number of papers, particularly in this country recently; such data are very interesting. For example, you find out really that, while notification rates are going down (slower than mortality, but they are going down) in Britain at the present time, the rates for new cases at age forty-five and over are nearly static, and those for males age sixty-five and over are actually increasing.

One can't entirely explain that all away by saying it is due to cohort changes and that we are really reaping the harvest of the past. It isn't entirely the explanation. But I think it has not yet been mentioned in this symposium that much attention has to be paid to tuberculosis in the older age groups, particularly in males. Those are the points I wanted to make on morbidity.

Dr. Cooper: Would you care to go ahead and discuss the question of tuberculin positivity as a means of measuring the problem, or would you rather put that off?

Dr. D'Arcy Hart: I would rather see if anyone else wants to comment on this.

Dr. Cooper: Dr. Canetti?

Dr. Canetti: I have nothing to add to what Dr. Hart has said; I agree entirely with him.

Dr. Cooper: Dr. Wilson?

DR. WILSON: I don't believe I have anything to add, either. I would agree and I would like to make one little comment about case registers. I think that we have paid a lot of lip service to case registers in this country, but there are very few case registers that really do what we want them to do. Perhaps in these well-developed countries (if that is what we call them) we should reach the point now where we really pinpoint the cases: where they are, what they are, and have an accurate record. I think we are ready to do it.

DR. COOPER: Dr. Perkins?

DR. PERKINS: I think that Dr. Holm's points are very valid. We still keep a weather-eye on the mortality rate, however, and it has been interesting to note that, although it went down precipitously when the new drugs first came in, it has leveled off. In fact, in a few places last year actually it went up a little bit, I believe, probably due to the Asian influenza outbreak.

In regard to morbidity, again I agree with Dr. Hart. In other words, ordinarily this is a very unreliable index. I think we pay more attention to it in the United States now than we did, because the Public Health Service was able to get the tuberculosis control officers to agree to standardize reporting with regard to active and presumably active cases and separate those from the others. By looking at those so-called "A" cases and also keeping an eye on the number of X-ray examinations per year to see that the case finding hasn't dropped appreciably, we think the rates are reasonably comparable from year to year. We are actually paying a little more attention to them than we did in the past, although admittedly they are unreliable for the various reasons Dr. Holm gave.

DR. COOPER: Now we will give Dr. Holm a chance at a rejoinder.

DR. HOLM: When I referred to the morbidity rate it was, of course, as Dr. Hart mentioned, the international comparison. I wish to give a warning because, over and over again, I see the tuberculosis problems in the different countries being compared by the morbidity rates, which mean quite, quite different things in the different countries. I think even within one country there can be a risk in doing it—for instance, in pinpointing the high prevalence areas. I think it is not enough to have the morbidity from the high prevalence areas. I think that actual prevalence surveys are needed.

Especially I wish to stress that there is one big risk in emphasizing the downward trend in mortality and morbidity. It gives the administrators who are allocating money toward the tuberculosis program an excuse for diminishing their support to the program. Therefore, I don't think we should stress this because I don't think that that gives the right index for the problem that is left.

DR. COOPER: Dr. Tucker?

DR. TUCKER: With regard to mortality, the only comment I would wish to add would be to point out what has not, I think, so far been said, that, as the mortality declines and we are now placing relatively less emphasis on this index and more emphasis on others, it has been partly our own fault that there has been a misapprehension on the part of the public as to the declining importance of tuberculosis because in the past we have placed so much emphasis upon the mortality figure and not balanced it with other indices.

With regard to the morbidity problem, very much along the lines of the comments that have been made, I would think that Dr. Holm and others would agree that, where it is possible to have a continuing, quite complete coverage of a closed group of individuals on an annual basis, it would be possible to have high significance from the morbidity figures; and I point out that within the Veterans Administration we do have this opportunity.

In the medical program of the Veterans Administration, for example, we have about 135,000 employees who are required to have annual physical examinations and X-rays, and tuberculin tests if tuberculin negative; and in this group, therefore, we are able to give, I think, quite accurate morbidity figures. Thus, what Dr. Holm was referring to, as he has now made clear, is quite a different problem. But under certain conditions, certainly, morbidity figures can be a very reliable index.

DR. COOPER: I think that should wrap up mortality and morbidity figures as to their importance in measuring the problem, and I would next like to go to the question of. . . .

DR. WILSON: I am not quite so sure about this now; wait a minute. We are dealing with a chronic disease here and not a disease that occurs during a year, like polio or like measles, and we have got to really say what we mean by prevalence. Have we got this distinguished from morbidity in our remarks? I don't think so.

Tuberculosis is a cumulative disease. For

instance, in Health District No. 1 in Philadelphia, we have been accumulating cases of tuberculosis. The case fatality rate has gone down. The morbidity rate has gone down a little—the annual morbidity rate—but the prevalence has gone up. So this is the figure that we should stress in tackling our tuberculosis problem, and I want to stress this before we get off the subject.

DR. COOPER: Stress prevalence rather than morbidity?

DR. WILSON: The number of people with tuberculosis, active, inactive, the number that need to have active supervision, and the number that still need to have lifelong follow-up.

DR. COOPER: I knew we would get into that.

Dr. Holm, will you pull us out of the hole?

DR. HOLM: What I referred to was not the thing Dr. Tucker mentioned, but the officially reported new case figure, which is usually referred to as the morbidity rate. There are prevalence surveys for tuberculosis. I mentioned that they were at present of the highest importance, exactly the type which Dr. Tucker mentioned, but we take randomly selected groups and let them pass a systematic examination and find out how many at a given time have tuberculosis; and this is, in my opinion, quite, quite different from the official morbidity rates.

DR. COOPER: Thank you very much for clearing up that point.

I think now are we ready to go ahead with tuberculin testing as a measure of the problem? I will first ask Dr. Perkins.

DR. PERKINS: I certainly agree thoroughly with Dr. Holm's comments all the way through. This matter of having standardized tuberculin is something we have been wrestling with. Dr. Feldmann has been getting the various commercial firms involved together with Dr. Seibert, whom I see in the audience, and with the Division of Biologic Standards of the U. S. Public Health Service, to try to work this out.

Dr. Holm, in a speech he gave Tuesday in New York, said that he had enough of a standard batch of tuberculin with which he could supply the whole world, including the United States, for ten years. As soon as we get back to the office, we are going to look into this because that is one of the problems, having a standardized tuberculin.

I might also say while I have the microphone that, through the cooperation of the Navy, Dr. Palmer has started routine tuberculin testing of all naval recruits. I think it is going to be extremely helpful to us in knowing where we are in regard to the prevalence of tuberculosis and the trends in the prevalence of tuberculous infection in the United States in the future.

DR. COOPER: Dr. Hart, would you take on from there?

DR. D'ARCY HART: I would just like to make two points. One borders on BCG, which we are going to consider later, but this is from a different point of view. One of the objections to using BCG wholesale in a community is that it removes the value of the tuberculin test. I only want to say that I feel that Dr. Holm's desire to use the tuberculin test as a way of judging the prevalence in a population where BCG is also going to be used can be met, to some extent at any rate, by compromise. This we have in Britain where mass BCG (and I am using that term advisedly; there is really no argument about using BCG in selected groups in contact) is applied currently to thirteen-year-old school children, to all who are willing.

That means that the tuberculin test from that point onward is useless. The program has been going five years, so you can say anybody between thirteen and nineteen at this moment may have positive tuberculin reactions due to BCG, but in those under thirteen it is still free, as it were. So, as Dr. Holm has said talking about 1 per cent at age fourteen, one can judge what is happening at age thirteen from now on in Britain because BCG only begins at thirteen, unlike some countries where it starts as a mass implement earlier. That is one point.

The second point is the plea that, if tuberculin tests are used for prevalence surveys, they shall not be restricted to one dose, such as 5 tuberculin units, but shall go up to 100 tuberculin units for the negative reactors, whatever interpretation may be put on the low-grade sensitivity. I think it is very useful to have this for the record and I will give a reason.

I have some figures for London: children age fourteen tested in 1950, and a comparable group in a similar area tested seven years later. The test dose was 3 tuberculin units followed by 100 tuberculin units as near as practicable. That is the same as 5 tuberculin units followed by 100. In 1951 the positivity was 26 per cent for 3 tuberculin units, and six years later it had fallen to 8 per cent—one third.

That is not the whole picture because, if you take the reactors to 100 tuberculin units only, that is, the ones who were negative to 3 TU,

they had doubled during that time. The 3 TU ones were one-third; the 100 TU had doubled.

We feel that that is a switch from high- to low-grade sensitivity by the tubercle bacilli, and without the knowledge of the 100 TU and the ability to make a total rate, which has diminished but not by a third (only by a small amount), we would feel we would have an incomplete picture. Let us get the figures and work out the interpretations at leisure afterward.

DR. COOPER: Dr. Tucker, would you comment on tuberculin as a measure of the problem?

DR. TUCKER: Before replying, may I ask a question?

Dr. Holm, I assume that from the public health standpoint, the health control standpoint, the value of the prevalence, as determined by the tuberculin test (by whatever technique) is based upon an assumption that this is the reservoir for clinical tuberculosis and that a certain percentage of tuberculin reactors may break down and become infectious. Or, am I wrong?

DR. HOLM: It is partly based on this, but also based on the fact that it will give an index of how many sources of infection there are around these children. If at the age of fourteen only 1 per cent react, that means that they have been able to live in the community for fourteen years and only have a 1 per cent chance of being infected, and the number of infectious cases or sources of infection must be very low indeed. It is upon this assumption of a correlation between the number of infections and the number of sources of infection that the value of the prevalence figures is based.

DR. TUCKER: Thank you, Dr. Holm. I think that does make it clearer in my mind. I had wanted to ask that question before stating that, in the Veterans Administration, among our 135,000 employees we have a thoroughly constant prevalence by tuberculin testing of 80 per cent positive. Now, the new people that come in have less but, working in a medical environment it is natural that they should have a higher conversion rate. I am completely in sympathy with the need for tuberculin testing as an index of prevalence.

DR. COOPER: Dr. Tucker, may I ask you a question? What is the conversion rate in the group that you are following from time to time?

DR. TUCKER: Twenty per cent of 135,000—these are the negatives—that is only 27,000. Then this should be broken down by age groups, and the rate of annual conversion is very low when we get into very small numbers. We are trying to accumulate more figures, so I am unable to give accurate figures at this moment except to report to you that, since this program began to be well organized (and I am sorry to say that was only two years ago), the rate of conversions of the negative reactors by half-year periods has been declining.

DR. COOPER: Dr. Canetti?

DR. CANETTI: Here again I agree entirely with Dr. Hart, and with other speakers, of course. I think that tuberculin testing is exceedingly important and is one of the most powerful weapons we have; but, of course, I firmly believe that we should not restrict tuberculin testing to one simple dosage and that we must use higher dosages in order to find out even weak tuberculin reactors, whatever the interpretation may be, as Dr. Hart and the others have said. There is no doubt that, at least in the western European countries, a great number of these weak tuberculin reactors are truly tuberculous people who have just very weak reactivity, and this is extremely important. It is even more important if we realize that, as on the whole the infectivity of surroundings is going down and the opportunity for reinfection is going down as well, the general trend of tuberculin sensitivity in the whole population will be toward lower reactions, and this makes it absolutely necessary that we use higher tuberculin dosages as well.

Another point which I would add to this which is entirely different is that we badly need tuberculin testing of populations of all ages, not only children, not only young adults, but adults and, of course, old people too. Things are changing and we must know what the trends are in the older groups, not only as to positivity and negativity, but as to the intensity of reactions.

The likelihood is that the general intensity of reaction will go down even among adults, and we have to know about that. It may be possible, although this has to be worked out very carefully, that, in the future, very strong reactions may be a source of tuberculosis cases, even in adults, and may be very useful for that. Of course, we don't know very much about that because so little tuberculin testing has been done for many, many years in adults, and the trends have not been followed.

DR. COOPER: Dr. Wilson?

DR. WILSON: No comment.

DR. COOPER: Dr. Holm, do you have anything further?

DR. HOLM: Nothing.

DR. COOPER: All right, I think then we can proceed to the final phase of this discussion which, again, will be broken up into a number of segments. What measures are at our disposal that will be effective in reducing the incidence and prevalence of this disease, and how effective are they?

Dr. Holm has listed those in three segments: vaccination, chemotherapy, and case finding. I would like to take up the first one, that of vaccination, and no discussion of BCG should go on without someone's paying tribute to our departed friend, Dr. Joseph Aronson, and I would like to officially do that for this organization.

Now, Dr. Holm, would you mind beginning the discussion of BCG and other vaccines, if any?

DR. HOLM: I think I have stated my point of view pretty clearly, so that I don't have to repeat it. I think it would be advisable to have Dr. D'Arcy Hart continue from there.

DR. COOPER: He was next in line. Dr. Hart?

DR. D'ARCY HART: I must try and fight against my tendency to be diffuse. Before starting I would like to say two things in case I forget. One is that I would like to echo what our chairman has said about Dr. Aronson. From the European standpoint, Dr. Aronson stands as the person who carried out the first and still one of the very few good control trials on BCG. One was always looking up his papers when the British Medical Research Council was designing their trial.

The second point is (a small point, but an important one) this: I don't know whether you do it in this country, but is it possible to get some way of finding out whether an individual has had BCG? After all, you have quite a few people given BCG, either those who want it or those in special groups. I have tried very hard in Britain to persuade the Minister of Health to have some sort of register. One would have thought it was quite a simple thing, but nothing has happened and more and more people are having BCG and have no idea they have had it. They even sometimes develop enlarged lymph nodes which might be thought by an enthusiastic doctor to be tuberculosis and could even be removed (it has happened).

It is obvious that it would be highly desirable if they could be labeled, but, like so many other things, it is part of the general vaccination and immunization problem of knowing whether anyone has been immunized. I should have thought that BCG was one of the easier ones; but if you could design a BCG register here, perhaps we would follow you.

In regard to the main question, I don't think this is the place to enter into a pro and con discussion of BCG. I think the best thing is to give just one final viewpoint. I think that my view is that one should divide up countries into different positions with regard to tuberculosis relevant to the desirability of BCG vaccination.

I accept the view that, provided you have a good vaccine, as Dr. Holm has said (what *is* a good vaccine is another matter), but a good vaccine anyway that will produce good protection in tuberculin-negative persons for at least some years, and that, again, may depend on how they are sorted out at the beginning. If you include lots of people with low-grade sensitivity by taking your tuberculin test for screening too low, and if you agree that low-grade sensitivity for whatever cause itself produces a protection or some degree of protection, you are obviously going to muddy your results by having protection on both sides of your line.

To what extent that is an explanation of some trials in which the protection is shown to be smaller than in our trial, I don't know. We took our screening test at 100 TU, but, even so, there are people who have a lower-grade sensitivity than that. But one really doesn't know. This may be the case and, therefore, in areas where there are other mycobacterial infections postulated and possibly actually discovered in the U. S. Public Health Service group, for example, in southern parts of the United States, this may make the thing even more difficult. I think we have less of this in Britain.

I adopt the hypothesis anyway that, under conditions such as obtain in many parts of the world, BCG can be protective. But even so, it doesn't necessarily follow that it should be used. It depends on other factors, such as the proportion of people in the population who are already tuberculin positive at the age at which you are going to vaccinate them and are, therefore, ineligible. It also depends on the amount of tuberculosis around.

There are so many factors, but I think one can

take it that, in countries where there is a high incidence of tuberculosis, there is a place for BCG at certain ages, theoretically at birth. In actual fact, even in countries with high prevalence of tuberculosis, such as India, there is a question whether it is really practical to expect to carry out mass immunization of infants and whether it may not be more feasible to start a bit later, perhaps at five years, and so on.

Passing from a country like India, you have the countries with an intermediate or fairly low prevalence, and I would classify our own country as having fairly low prevalence, yet we feel that BCG is useful (I am talking about mass use now). As I said before, we give it at present on a national scale, voluntarily, at age thirteen.

I would like to answer the question of whether, if we hadn't started in 1952, we would start at this moment. We did start in 1952 and I think there is nobody in Britain who is urging that it be stopped. There are a few people, including some in my own unit, who would like to have had it start a few years earlier so as to catch some of the people already tuberculin positive at thirteen and give them BCG before that; but at the moment I think most people are satisfied that this is not a bad time, age thirteen. If, as our trials seem to suggest, the immunity lasts until perhaps twenty years at least (those are not published figures, only suggestive), then it means that we can get away with one tuberculin test on a mass basis during life and not have to do a repeat. That, of course, from the point of view of the expense will be a very great convenience.

This represents a compromise in our country where we regard the incidence of tuberculosis as fairly satisfactory, but not one of the best. In a country like Denmark, where the incidence is lower, even they are continuing with BCG, but changing the age a bit and using the same age group as we are, raising it, according to Dr. Holm, from age seven to age fourteen, which is very similar. I think that is probably going to be the pattern in a number of European countries.

I am not sure what happens in the United States, which is in a little better position at the moment than Britain, on the average, but not quite as satisfactory as Denmark. I am certainly not going to try and tell you people what you should do. I think it is a very difficult problem, and Carroll Palmer and I have many arguments which continue every time we meet; and if he is not here, I would rather end at this point.

DR. COOPER: Thank you very much.

Dr. Canetti, would you comment on this?

DR. CANETTI: I am in the strange position of being always entirely in agreement with Dr. Hart, so this is very uncomfortable because I must always start by saying I agree. I think I agree with his statement, but I would add a word on this: that the use of other vaccines which are more or less produced in different parts of the world experimentally, all of these other vaccines up to now consist of mycobacteria which are living and which, injected into animals, produce a certain degree of immunity but also sensitize the animal just as BCG does.

I don't see any point in changing the vaccine because in all likelihood the degrees of immunity which can be involved by such microorganisms cannot be significantly or to a very great extent different from that of BCG. There might be slight differences, but not more, and all these vaccines have the same inconvenience in my eyes and in everybody's eyes, which is to induce hypersensitivity.

The real change in vaccination would occur on the day a vaccine would be produced which would induce immunity but no allergy, no hypersensitivity. As we might expect, such a vaccine is not an open problem. If the immunizing constituents of the bacillus are isolated with sufficient techniques, if they can be isolated and prepared in industrial quantities, and if they prove really vaccinating, they probably would not induce hypersensitivity; and this would be a great change and a real advantage. I can't elaborate upon that, but the obvious reason would be that with such a vaccination immunity would be induced; but if infection occurred, it could immediately be detected by the change of the tuberculin reaction which, as you know, is not the case with BCG. Until that day, if it ever comes, I think there is no great use in experimenting with other vaccines, at least on a great scale.

DR. COOPER: Thank you very much. Dr. Wilson?

DR. WILSON: Dr. Hart is our guest who is unwilling to suggest a plan for the United States; but, of course, the American Trudeau Society has offered such a plan which has in essence been endorsed or repeated by the U. S. Public Health Service, namely, that those should have BCG who are at hazard due to their profession, their training, or if the person is a child in a household

where there is tuberculosis. So we do have a plan for the United States.

DR. COOPER: Dr. Tucker?

DR. TUCKER: Three quick points, Dr. Cooper. The Veterans Administration policy with regard to BCG vaccination is to offer it to its employees on a voluntary basis and to make it available should they care to have it. There is no requirement, of course, that they take it. A limited number of employees avail themselves of this opportunity.

My second point is this, that as a medical educator and clinician in the past I have personally been convinced for a long time of the value of BCG in this country for high-risk groups and have recommended it. However, in recent years I have begun to wonder whether it may not be more meaningful to approach this particular problem in such limited groups of individuals through the chemoprophylactic approach. And so I am personally, in the environment in which we work professionally, less convinced even than before of the value of BCG in this country even for high-risk groups.

The final point is that, if we could come up with a drug which would sterilize tuberculous infection when it occurs or if we could—even better yet—get a depot drug to prevent tuberculous infection, this would be better than any vaccination.

DR. WILSON: May I comment on Dr. Tucker's comment? It seemed to me, listening to the panel the other day—the first panel on primary prophylaxis with Dr. McDermott as chairman—that every member in that panel came around to the point of view that, if the individual is protected by the administration of a drug, primary prophylaxis, and is still at risk at the time you want to discontinue the drug, you should then give him BCG.

I wonder, Dr. Tucker, if a person starts medical school and starts to receive his isoniazid (or whatever drug is being used when he is a sophomore in medical school) let us say, when he goes into physical diagnosis and first gets into contact with patients or into pathology with a cadaver, when would you stop the drug? At the point when he is graduated from medical school? At the point he finishes his internship? At what point?

DR. TUCKER: I wouldn't do it that way.

DR. COOPER: How would you do it, Dr. Tucker?

DR. TUCKER: Not having demonstrated that there is a drug which prevents infection or even that necessarily controls it, and particularly avoiding the question of BCG after discontinuation of drugs, it is my present preference for these members of the high-risk professions (I am thinking particularly of medical students, physicians, nurses, and so forth, working with patients) to follow them with serial tuberculin tests until a positive reaction is found and then employ isoniazid. I would employ isoniazid for very long periods of time, by which I mean two to three years, and then continue to watch the subjects for a long time.

DR. D'ARCY HART: Could I ask a question of Dr. Tucker? I want to be quite clear that for tuberculin-negative persons entering a high-risk group you still think you would not give BCG, but you would wait until they became positive and then start giving them isoniazid; is that so?

DR. TUCKER: Yes.

DR. D'ARCY HART: Is it the agreement of the panel, then—I would like to take this back to England—that there is nowhere indicated in the United States the use of BCG on, shall we say, school children *en masse* who have not necessarily a known contact with tuberculosis, and that goes for areas like Puerto Rico?

DR. COOPER: Dr. Tucker, would you start off on this?

DR. TUCKER: I was speaking, of course, only for medical members of these groups that I mentioned in which there is the opportunity for adequate supervision. There are certain other circumstances in which I still believe that for high-risk groups BCG is quite proper.

DR. COOPER: Is that a definite answer to Dr. Hart's question?

DR. D'ARCY HART: I would like to know what the others think.

DR. COOPER: Dr. Perkins?

DR. PERKINS: Officially my stand must be that of the American Trudeau Society, which does recommend BCG for specialized groups but special-risk groups only, not any mass immunization of any given age.

That coincides with my own opinion, too. I think, personally, that that is right where we should be at the present time. I did not influence the American Trudeau Society in that statement; I wasn't even present at their last meeting when they discussed it.

DR. COOPER: Dr. Wilson, what is your stand on Dr. Hart's question?

DR. WILSON: I don't think at the present time that there is any place in the United States where mass vaccination, either of infants or of school children or of any other group, is indicated.

DR. COOPER: How about Puerto Rico? Aren't there studies going on there?

DR. D'ARCY HART: I believe I wouldn't be libeling Dr. Palmer if I said that the studies would lead to their not suggesting mass vaccination rather than suggesting it.

DR. COOPER: Dr. Canetti?

DR. CANETTI: I beg your pardon. What was the question?

DR. COOPER: Dr. Hart wanted to known (of course, you are not from the United States, so I am not sure whether you should qualify for a vote)—he wanted to take back a statement to England from the States in regard to whether or not there was any justifiable reason in the States for mass inoculation with BCG. I guess you can't vote on that. And Dr. Holm is disqualified, too.

I would agree that there is no such justification in this country that I know of.

I think at this point I have exhausted my panel, but I would like to call on my auxiliary panel. I see Dr. Middlebrook down there and I would very much appreciate it if he would comment on this use of BCG and other vaccines.

DR. MIDDLEBROOK: Thank you, Dr. Cooper.

During the past six or seven years, starting when I was working at the Rockefeller Institute, I developed an increased interest in problems of immunity and decided that the air-borne route of introduction of mycobacteria into animals would be a very profitable method for studying problems of immunity.

Fortunately, we have been supported in this work by several grants from the American Trudeau Society of the National Tuberculosis Association. We have been able to approach the problem from a dual standpoint. It was in 1953 that I asked for support from distinguished individuals for an isoniazid prophylaxis study to be carried out at a state hospital in Colorado. Apparently this was far too premature and I got absolutely no support for this; and yet I continued to have interest in the possibility of isoniazid prophylaxis and immediately put it into practice in my department, which has had between forty and fifty-five people.

I have had an experience which makes me look somewhat askance at the possibilities that might be offered and practiced of using isoniazid prophylaxis either in the sense of primary prophylaxis, as Dr. McDermott defined it on Thursday, or as secondary prophylaxis in any wide degree in this country or elsewhere. My reason for this is the difficulty to which Dr. Hart referred, which is a matter of keeping records, of being sure that everyone gets his repeat tuberculin test every three or four months.

Now, it should be simple in my department with only forty to fifty-five people to get this done and to administer drugs should the employees become positive reactors, which has been in some five instances in five years. But it isn't. It isn't easy even under these apparently well-controlled circumstances, so that I became even more interested in problems of immunity.

Recently, during the past two years, we have followed up what amounts to a chance observation. Using air-borne infection technology, we observed and were quite surprised to observe that it takes no more than one or two bacterial cells, single bacterial cells of a good BCG vaccine strain, to initiate an infection in guinea pigs which results in a level of acquired resistance in those guinea pigs as great as can be achieved by the subcutaneous inoculation of a million bacterial cells, for example. If one allows each guinea pig to inhale ten bacterial cells, that guinea pig will become as immune as he would if he inhaled a hundred times as many, say a thousand.

I emphasize guinea pigs because human beings simply aren't guinea pigs, and all of the theoretic considerations, all of the observations which are made in guinea pigs, might not apply to human beings. However, should it turn out that an individual human being could be infected with BCG, with that self-limiting infection which BCG confers, with a minimum of ten to a hundred bacterial cells inhaled, this would provide some advantages over the intracutaneous inoculation, introduction of living attenuated organisms in human beings.

The first of these is one which is quite relevant to the problem of what vaccination does to the skin tuberculin reaction. Several experiments made many decades ago and subsequently have shown that the introduction of an antigen which causes a delayed type of hypersensitivity (and killed tubercle bacilli have been used, for example) into the skin, results in a greater degree of skin hypersensitivity than the same amount of

antigen introduced intramuscularly or intravenously. No studies have been done by introduction of the antigens by the air-borne route that I know of, but there is the possibility that the level of skin hypersensitivity for the same degree of immunity may well be much less after BCG vaccination by the air-borne route in human beings than the same level of immunity induced by introduction of the organisms by the intracutaneous route.

I might suggest something rather amusing, namely, that the practice of oral vaccination, which is so widely carried out in South America and which was actually recommended, as you recall, by Calmette himself, may well be achieving its effects primarily by the air-borne route, by inhalation of the droplets of BCG which are certainly present in the room while several children are being vaccinated; and it may well be that this is in fact the principal mode of vaccination by that method.

Surprisingly enough, we did not think of this (not being intelligent enough) until after we had completed several months of work with BCG by the air-borne route.

DR. COOPER: Thank you very much, Dr. Middlebrook.

Would anyone else on the big panel wish to comment on this? If not, I would like very much for my panel to comment on Dr. Middlebrook's comments.

Dr. Canetti?

DR. CANETTI: I have nothing to add because I think air-borne vaccination is certainly worth studying, and I think these studies of Dr. Middlebrook would be very helpful, although I don't know whether this could be applied practically; this is another problem. For the mechanism of induction of immunity, this might be extremely interesting and helpful, but whether in practice some immunization can be given is another problem.

DR. COOPER: Anyone else? Dr. Hart?

DR. D'ARCY HART: Only following the delightful idea of Dr. Middlebrook that really successful vaccination has been due to the small amount getting in through the lungs. Is that what you were suggesting? You were suggesting that the effective part of vaccination might result because a few droplets got through the lungs while the main part was being injected into the skin; is that right?

DR. MIDDLEBROOK: No, they swallow it.

DR. D'ARCY HART: I thought you meant that some was coming off the syringe. You don't feel that that is enough?

DR. MIDDLEBROOK: Oh, no, I didn't think of that. Maybe that is true.

DR. COOPER: Dr. Burke?

DR. BURKE: I feel that I should make one or two comments. My home is in the Province of Quebec in Canada. We have three and a half million people in the province. The public health authorities, recognizing that tuberculosis is still a very prevalent disease in our community, have recommended that all newborn babies be given BCG vaccine and that all school children whose parents are willing to allow them to have BCG vaccine be given BCG.

This program has now been in progress for five or six years. I have no results to give you from the program. Our circumstances may be a little unusual in some ways. Only a very few years ago we obtained enough beds to admit to the hospital the people with active and open tuberculosis. Unhappily, we still have a good many people who leave the hospital against advice, with positive sputum, and who wander around in the community. In our case, then, I think there are special reasons for mass BCG vaccination of selected groups.

The other point that I would like to make (and this is very personal) is that I myself have long been interested in how vaccination may work, and I realize that we do not know very much about what happens between the time when the tubercle bacillus enters the human body or enters the animal body and the time when the individual becomes a tuberculin reactor.

I am not going to attempt to give you an account of our experiments this afternoon, but I am going to summarize things by saying this: that, if we take little groups of nonvaccinated guinea pigs and vaccinated guinea pigs and we instill suspensions of tubercle bacilli into the nares of those guinea pigs, there is a tremendous difference in the rate of dissemination between the nonvaccinated and the vaccinated within a period of eight days. As a matter of fact, it is detectable in one day.

Because I have an unusual approach to the problem, we are looking in places other than the ones where people normally look for dissemination in both these nonvaccinated and vaccinated guinea pigs; and we all hope that some time in this year 1959 we will have something to report,

from an experimental viewpoint entirely, that may shed a little bit of light on the place of vaccination or immunity in the prevention of tuberculosis.

DR. COOPER: Thank you, Dr. Burke.

DR. CHAPMAN: Dr. Cooper, I would like to comment on Dr. Middlebrook's observation, if I may. This is getting pretty far afield. You may recall that at the time of the Lübeck disaster, when the wrong cultures apparently were used, in surveying those children a large number of them were found who showed perfectly enormous pulmonary lesions. In trying to explain how they got these lesions, it was recalled that the German nurses who administered the vaccine orally held the child's nose while he tried to swallow and he aspirated a fair amount and this is supposed to have accounted for it. So I suggest you might try it that way, Dr. Middlebrook.

DR. MIDDLEBROOK: This is fascinating.

DR. CHAPMAN: There are some reports of X-rays, and so on, shown of those children.

DR. MIDDLEBROOK: Apparently some punitive public health people do that in Brazil, but I am sure that those guests who are here from Brazil would not agree that anyone should hold a child's nose unless it was absolutely necessary. It would be possible, however, that, even if they did not hold the childrens' noses, the introduction of droplet nuclei into the air would be sufficient to permit the inhalation of the very few bacterial cells sufficient to induce the primary self-limiting BCG infection.

DR. CHAPMAN: I think it can be tried very simply, don't you? In one group you hold the nose and in the other you don't!

DR. COOPER: May we conclude, unless there are other comments from the panel, that at our present state of knowledge perhaps the route of use of BCG is still parenterally.

Dr. Perkins?

DR. PERKINS: I just wanted to say that it did my heart good to hear Dr. Canetti say that there might be a possibility of a vaccine which did not produce hypersensitivity. I think we all must agree that, if we had that type of vaccine which we have been talking about for so many years, one that doesn't produce hypersensitivity and produces immunity cheaply and safely and innocuously, that would be *the* program and we would all be in agreement again.

DR. COOPER: But at the present writing we have no such vaccine.

DR. WILSON: May I make one little comment on that? If we had such a vaccine today in the laboratory, how many years would it take to find out whether this was an effective vaccine or not in human beings?

DR. PERKINS: An excellent point, of course; and you couldn't find out in this country, as Carroll Palmer has been repeatedly pointing out, and you would have to go elsewhere. But I think you still could find enough material elsewhere and get an answer, I should think, in not too long a period of time, although someone better versed in this field than I might reply to that.

DR. CANETTI: Of course, we have to rely on experimental work but, if such a vaccine would induce good immunity in guinea pigs and other species, there is no reason to believe that it would not induce a certain amount of immunity in man.

DR. WILSON: What I meant to imply was that we can test with a tuberculin test for the fact that the person has had BCG effectively, but we have at present no serologic or other test, as far as I know, to tell whether a person has become immune to tuberculosis.

DR. CANETTI: I think that, with such a vaccine, there would probably be antibodies which could be detected by different methods, and this would give at least a sort of rough insight into the immunity existing in such a patient.

DR. COOPER: Are there any further comments or questions? If not, I think we can leave it at that point, because we have a lot of ground to cover yet, and go to the phase of chemotherapy or chemoprophylaxis, preventive chemotherapy, and its place in the over-all program.

I think it has been stated that everyone agrees that obvious tuberculosis should be treated. What is the place of chemoprophylaxis in an over-all program? I think perhaps I will start with Dr. Canetti this time, if he wouldn't mind commenting.

DR. CANETTI: Let's put it briefly because, after all, we were speaking about that Thursday. I think chemoprophylaxis has a definite place, either primary or secondary, but only in very special circumstances. As primary chemoprophylaxis it should be given only in cases in which a strong positive case exists which can't be broken up. It should be given for the time the contact exists and, of course, vaccination should be performed. After all, one has to help the organism to build up a real active immunity, so this is only for very special circumstances.

As to secondary chemoprophylaxis: that has a place also for infants, very recent converters at special ages, and so on, but I would emphasize one point which I think has not been emphasized enough in the problem of chemoprophylaxis. I think we have to look for chemoprophylaxis for a short period because, if it comes to chemoprophylaxis for a year, or something like that, this is not chemoprophylaxis; this is administration of a drug for perhaps as long a time as the disease which this drug should prevent would last, as long as the treatment of this disease would last.

We can't think of prophylaxis as lasting as long and costing as much as the treatment of the disease itself, so chemoprophylaxis in tuberculosis, in my opinion, can only have meaning if a short-term chemoprophylaxis can be efficient. This, of course, we don't know yet because no work has been done along these lines. How long I can't say, but I think that more than three or four months' chemoprophylaxis would be a sort of irrational thing.

DR. COOPER: Dr. Holm has reminded me that I misread his statement, "chemotherapy treatment in a mass program of prevention." I would like him to take that a little further, if he would.

DR. HOLM: What I tried to state in my introductory remarks was that I don't think we have any big problems about true chemotherapy in the future program because all definite diagnosed cases should be treated. Also, I stated that our present knowledge of real prophylaxis does not permit us to put that on a mass scale.

The problem I really raised was concerning what I considered prophylactic *treatment*, which was treatment of patients who have signs or symptoms that may indicate that they might have tuberculosis; that is to say, that they belong to a group in which there is a considerable probability that they will eventually develop a real case of tuberculosis; and I suggested that these patients should at present systematically get treatment with isoniazid for one year.

DR. COOPER: I would like to hear the comments of, first, our own panel in regard to Dr. Holm's statement. Dr. Wilson, would you start?

DR. WILSON: At one meeting I attended in the West it was suggested that all of those who have had tuberculosis and had been treated in the past be called in and given a year of treatment with isoniazid. I rather reject this broad program as being quite outside of our reach to accomplish, even in the United States. It certainly would be way outside in other countries. This would be the same as treating everyone with a lesion in the apex believed to be tuberculous and with negative sputum. I think it would probably be better to wait and watch these people and treat them if they showed symptoms. I just don't know what you would accomplish by a year's treatment of an X-ray shadow.

DR. COOPER: Dr. Holm, would you like to comment on that?

DR. HOLM: I think it was stated in the panel yesterday that by observing patients who have had lesions in the lung it was found that 30 per cent of them developed tuberculosis within a stated period. My suggestion is that such a group, in which there is a 30 per cent chance that each individual may get tuberculosis within the coming few years, should have what I would call prophylactic treatment of tuberculosis, prophylactic because we don't know which of the hundred patients has tuberculosis. However, I would be prepared to treat a hundred people with isoniazid for one year, even if only twelve really benefited from it, on the assumption that the twelve really would benefit because these would be really early cases without cavities.

DR. COOPER: Dr. Hart?

DR. D'ARCY HART: I would like to say two things. First, I take it from Dr. Holm that these are cases in which roentgenographically there is a suggestion that it is tuberculosis, but it is unproved bacteriologically; is that right?

DR. HOLM: Yes.

DR. D'ARCY HART: This is where British (and I think many other countries too) differs from Danish perfectionism, because I think in many clinics in Denmark they would not agree that there is a case of tuberculosis unless it were confirmed bacteriologically.

It was said in an earlier panel that not everybody was in agreement on that and, if you assume that you can have common tuberculosis when you cannot at that time find tubercle bacilli, then this just falls into the group of plain treatment. In any case, I would like to abandon the use of the word "prophylaxis" for this sort of case in which there is already a lesion. Otherwise we should start having ordinary treatment of tuberculosis, full-blown, called prophylaxis because, after all, you are trying "to prophylact" against death, aren't you?

DR. COOPER: I don't want to get mixed up in the semantics of Thursday morning.

Dr. Tucker, would you comment on that phase?

DR. TUCKER: I will very happily try to avoid the semantic problem. If I have understood Dr. Holm correctly (perhaps in an attempt to try to simplify this), he has advocated or raised the question whether isoniazid might not be used in three different situations: one, about which we have talked, the patient who probably has tuberculosis, but it is unproved probably on the basis of clinical criteria, including X-ray criteria. Second, he has raised the question here for those individuals with no signs or symptoms of tuberculosis except positive tuberculin reactions and states there isn't enough evidence to advocate prophylaxis at the present. Third, he does, I believe, advocate it for the recent tuberculin converter.

I would add a fourth group in which we might raise this, and actually I am doing so because in Panel Two on Thursday we didn't have time to raise this question. At the meeting we had beforehand, Dr. Aaron Chaves quite properly questioned whether there might not be a place for what may be called prophylaxis for those patients who have had active tuberculosis adequately treated and in whom the disease has become inactive but who have some special nontuberculous medical problem.

This is a special type of prophylaxis, thinking of diabetics, thinking of patients with forms of malignancy (including leukemia) in which steroid therapy might be used, and patients with emphysema, elderly patients when there may be a relationship between these nontuberculous conditions and a reactivation of tuberculosis.

My over-all reaction, Dr. Cooper, to these is that we desperately need more information as to the value of what might be called prophylaxis in these several situations, none of which is exactly similar.

DR. COOPER: Dr. Perkins?

DR. PERKINS: This is a little outside my field, but I found what I though was some inconsistency here that I would like to clarify at any rate. With regard to this first group you are talking about, those who have X-ray lesions which you can't prove bacteriologically to be tuberculosis, you said nothing about a tuberculin test there. Perhaps that goes along with your idea of BCG immunization, and your tuberculin test is no good.

In this country I would think you would do a tuberculin test and, if the test was negative when it was properly conducted, then you wouldn't bother with treatment, because you would know certainly that tuberculosis wasn't present.

Then when you say that there is the possibility of treating those who are merely reactors or early converters, there again it seems there is some inconsistency between your previous suggestion of mass immunization with BCG. How are you going to know they are recent converters since everybody is going to be tuberculin positive? Perhaps I am being a little unfair here.

DR. HOLM: What I suggested for a large part of our elimination program was vaccination of the adults, but it would still be the children who would be tuberculin negative. And I am thinking of the converters at that age. Exactly for the reason you mentioned, that all of the adults in the several countries I am thinking of would be tuberculin positive because of vaccination, we would have to rely only on the X-ray.

But altogether, I think that the tuberculin test in adults is not too widely used, so that the risk of giving isoniazid to a person whose X-ray was not normal, even if he had no tuberculous infection at all but only had a BCG vaccination, the risk would not be too great and the inconvenience too important.

I think the reason why I am proposing this is that, if we are going for a real program for elimination of tuberculosis, we must make sure that we treat all cases of infection, all infectious cases, all sources of infection, and prevent as many sources of infection as possible. The question is whether we are ready to go into that. If not, it is not, in my opinion, a program aiming at elimination of tuberculosis as a public health problem, but only a tuberculosis control program aiming at diminishing the morbidity and the prevalence as much as we can.

DR. COOPER: Dr. Wilson, do you have any thoughts on this?

DR. WILSON: According to the figures that Dr Edward Blomquist brought back from his trip to the Scandinavian countries, the proportion of patients picked up in the minimal stage over there is very much greater than it is in this country, and apparently people in those countries go through a much longer period of being in a minimal stage. I think our experience here in Philadelphia, with the population we deal with, is that very many patients spring from showing no evi-

dence of tuberculosis in the small film and the large film to full-fledged far advanced tuberculosis within a relatively short period, so that I don't think we have quite the same group to deal with that they have in the Scandinavian countries in this regard. There are some differences in population or behavior of tuberculosis here.

DR. COOPER: Dr. Hart, do you have any further comments?

DR. D'ARCY HART: No.

DR. COOPER: I would like to confirm and go along with Dr. Tucker on the idea that there is another place for prophylaxis. That is, when you are using steroids for other diseases, if the individual is tuberculin positive, he should have isoniazid. I deal with patients and not the mass.

That brings us to the final phase of Dr. Holm's questions, and that is the place of case finding. Unfortunately, I was not here yesterday afternoon and wasn't able to get their summary of case finding. Dr. Floyd Feldmann was on the panel, so, Dr. Feldmann, in introducing this subject would you mind summarizing their conclusions yesterday afternoon or any special points you would like to bring up?

DR. FELDMANN: I did not take the precaution of writing anything down yesterday and, as I recall it, we did not have a complete summary of all forms of case finding. We did introduce some ideas which have been covered partially here already in relation to certain high-risk groups, and we laid a little basis for that by taking the general shape of the curve of tuberculin reactors in the population and from that derived some idea of what the risk rates were at various ages. Going on from there, it was suggested that there were many other things determining the risk beside the age, such as the sex. We know from other studies that you can have certain groups in certain situations in which you can get at them more easily than others, for example, in institutions. I don't think I need go through all that, but we know that they are very definitely high-rate groups which can be reached easily.

The general feeling was that at this time the tuberculin test could be used to great advantage more than it had been in the recent past, but that the X-ray was extremely important in case finding and that we shouldn't let some of the fears of radiation hazards deter us from using the X-ray to its full advantage.

I realize that is not a very coherent or complete summary, but those are at least some of the things we talked about.

DR. COOPER: Thank you, Dr. Feldmann.

Dr. Hart, would you comment on case finding as a tool in tuberculosis eradication or control?

DR. D'ARCY HART: My only comment is to say that I don't think that there has really been agreement on the best way of using mass roentgenography, and that there probably are much better methods than we are using at present. In Britain, although I believe it is taught here by some people that the National Health Service has introduced a uniformity, you can find enormous differences in areas in the way mass roentgenography is being used because it is left to local option; and there is really lack of agreement about the best way. I expect that is so here also.

For example, if we were going to be "Public Eradicators Number One," we would want to make an absolutely stupendous effort, as they did in Glasgow, Scotland, recently, and try to get a much larger proportion of the population in the net than ever before. There they got 70 per cent. That may not seem too wonderful, but it is incredible for a population of about two million as tough as the Glaswegians. That was done by superhuman efforts which could obviously not be repeated again for several years. But I suppose if we all set about it and we all thought it was worth while (on which I don't think there is agreement), we could by stupendous efforts do the community type of survey which Dr. Holm mentioned and not think so much of whether we do factory groups, how often we do them, and whether we travel around or whether we have static units.

If we made an enormous effort like that, I daresay we could get a much larger proportion in the net. The question is whether it is a good thing and whether it is too expensive, or whether that is the best way of expending our energy. Certainly, if we got an enormous proportion, presumably we would diagnose a very much larger proportion of cases that are around and we could treat them.

DR. COOPER: Dr. Tucker?

DR. TUCKER: It is perfectly obvious to all of us, of course, that we cannot really control tuberculosis unless we can find the case which is infectious and capable of disseminating the bacillus before the harm is done. The problem, then, is not so much the techniques as how to apply

these techniques without employing dictatorial methods.

I shall refer only once more to the captive group of Veterans Administration employees. In these 135,000 employees of our system, where we do have the opportunity to require certain examinations along these lines, the incidence of new active cases per year has fallen to between two and four per 10,000 per year. This is a very low rate and it has been dropping year after year.

This demonstrates that not only is it possible to have good case finding under these dictatorial methods, if you like, but also that with such methods one can find the cases and have the whole program of tuberculosis control. I don't know the answer, short of dictatorial methods, as to the best method. This is for the public health people to work out. Certainly from the standpoint of what is desirable, if we could have adequate examinations (and this is really an essential part of our program), this must be done.

DR. COOPER: Dr. Wilson?

DR. WILSON: I don't have any comment on this point.

DR. COOPER: Dr. Chapman?

DR. CHAPMAN: As far as your program of eradication is concerned, Dr. Holm, it seems to me that one of the vital constituents of this has to be continuing public interest and support. As tuberculosis becomes less common, this is going to be a real task. I think the goals are worth trying for, but I think that the things which have been talked about here, like getting everyone tuberculin tested and everyone X-rayed, have never happened anywhere. It is going to be awfully hard to sell this sort of thing in a diminishing problem in the United States. Across the world I would imagine the same thing would happen, that people get frightened by panic situations for a while, and they recover.

This is a real problem which probably isn't all medical, but it is somewhat epidemiologic and, if you can find a way out of that dilemma, let us know.

DR. COOPER: Dr. Holm, do you have a comment?

DR. HOLM: This is exactly one of our difficulties, that it is difficult to keep the public interest up for a long period. This was exactly the reason why they systematically adopted a different method in Scotland than is used in most places. They decided to take an area, for instance, as big as Glasgow and in a very short time do extensive publicity; and within five to six weeks 700,000 in Glasgow were examined by a big number of X-ray units. What we got out of this was really impressive.

In the years before, about 2,000 cases had been diagnosed every year, reported every year. During the mass survey they found more than 2,500 infectious cases unknown and unreported before. So this might be one of the methods; but, as I stated, I think we have to look into the problem of how to organize these community screenings so that you get very close to 100 per cent.

DR. COOPER: I was hunting for a Public Health Service representative, knowing that a few years ago they conducted these city surveys in the larger cities in the country, but I don't seem to be able to spot one. I told Dr. Perkins that he was the closest thing to a Public Health Service man that I knew of.

DR. PERKINS: I wish somebody were here from the U. S. Public Health Service. We did have these extremely big case-finding rapid surveys in the large cities which I think were worth while. There was a lot of criticism of them, but they certainly found a lot of cases that had not been known previously to the health departments. I personally feel they were discontinued too soon. When the new drugs came out, Congress suddenly decided that tuberculosis was all over and they just cut those out before we had a chance to get work done in Washington to try to save them.

We did save the rest of it in appropriations, and we have kept the appropriations up pretty well since then; but I doubt if we will ever go back to that. I just don't think it is in the cards for the United States from this point on. Now, with our attempt to be more selective in our case-finding programs and with this apparently greater apprehension here about radiation hazard than exists in almost any other country, I doubt if we will ever go back to these big city-wide surveys.

I would like to have someone else comment on that, perhaps Dr. Feldmann.

DR. FELDMANN: I think the main reason that we would not go back to big city surveys in this country is that the yield in this country is small. It would never be anything near the yield which was obtained in Glasgow, and that is why we have gone to a more selective program.

DR. COOPER: I would agree that I think they served an awfully good purpose at the time and I doubt if we can ever get back to them. Whether they were stopped too soon or not, I don't know.

We have used up our time and I debated with Dr. Holm as to who would try to summarize, and his last comment to me was "perhaps we'd better leave them where they are." I think maybe he has something there!

Before concluding this meeting, I would like to thank the panel for their help and cooperation and actually for putting on the show; the big panel and the audience, for your patience. Thank you very, very much, and this concludes the meeting.

GLOBAL TUBERCULOSIS ERADICATION

JAMES E. PERKINS[1]

I am sure you will agree with me when I say that the past two days of meetings have been most enjoyable and profitable. On behalf of the National Tuberculosis Association I should like to extend my sincere thanks to the Board of Trustees and Administrative Committee of the Deborah Sanatorium and Hospital for presenting this International Symposium on Tuberculosis. Your planning committee, headed by Dr. George Sommer, has done its job well.

I am sure all persons interested in promoting sound control programs will share my sentiment when I say, "Congratulations, Deborah—and may any future symposia sponsored by you in other fields be of comparable top quality!"

May I also say that in the tuberculosis field alone there continues to be an important role for an institution like Deborah, which offers a place for those ill from tuberculosis and other serious, prolonged diseases of the chest and who may have been unable to get elsewhere the care they need. Deborah may well be proud of its thirty-six years of humanitarian achievement.

This symposium fits into the "teamwork pattern" of tuberculosis control which has developed so effectively in our country during the past fifty years or more. Aside from certain scientific and medical considerations, one outstanding contribution to the continuing progress being made in the battle against tuberculosis is the high degree of teamwork between agencies and organizations—official and voluntary—and between individuals representing many disciplines and fields of activity. As most of you know, the concept of the physician and layman banding together to promote a common health cause, and to achieve a common health objective, originated in this State of Pennsylvania. Here was formed the first tuberculosis association in this country before the turn of the century, and the concept that was developed here was also the guiding principle in the establishment of the first voluntary national health agency in the United States, the National Tuberculosis Association, in 1904. It is appropriate, I think, in this connection to point out that the Pennsylvania Tuberculosis and Health Society, as well as the tuberculosis associations of New Jersey and Delaware and the National Tuberculosis Association, were happy to lend their names in endorsement of this excellent symposium, and are well represented in the audience.

How richly this concept of teamwork in tuberculosis control has paid off! Since becoming Managing Director of the Association almost eleven years ago, I have visited every state of the Union and many countries; and it has been a source of great satisfaction to observe this same spirit of cooperation in many places, throughout this country on the state and local level, between the National Office and its medical section, the American Trudeau Society, and the National Conference of Tuberculosis Workers on the national level, as well as with the U. S. Public Health Service, the Veterans Administration, and other national agencies; and between the voluntary International Union Against Tuberculosis and the official World Health Organization, on the international level. Certainly these cooperative efforts mean more rapid dissemination of the latest scientific information, better medical and auxiliary services for our tuberculous patients, and better protection for our communities.

* * *

In the time remaining at my disposal, I should like to place before you a challenge for the future. It is a daring one, and some may say unrealistic. However, when we have been blessed to live in an age of scientific marvel and have been able to witness so many advances in recent decades in the communicable disease field, who among us can say that any goal in the infectious disease area is impossible?

The challenge which I want to throw to you this evening is the suggestion of a formal concentrated program of eradication of tuberculosis from the whole face of the earth!

No doubt the first question to arise in your mind is what do I mean by "eradication"? I see no reason to pull any punches in this matter. I mean the ultimate goal of having no human being on this

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earth react significantly to a skin test with a proper dosage of a standardized tuberculin; in other words, total bacteriologic eradication so far as tuberculosis is concerned.

I have no illusions, I assure you, as to the magnitude and difficulties involved in such a program. I am quite aware that to date no communicable disease has been eradicated through man's efforts. I know there are many who doubt that specific antituberculosis control measures have been of any appreciable significance in the reduction of the tuberculosis problem to date and feel that we are merely in the trough of one of the great cycles of tuberculosis which ebbs and flows through the centuries. I know that even the tubercle bacillus is not an entity. I know there is grave doubt that we have seen our last world war—or even in the absence of such a cataclysm, doubt that it will be possible to achieve or maintain standards of living essential to a continued reduction of tuberculosis to the point of complete elimination. And I could name many other real, or theoretic, obstacles.

On the other hand, I also believe that man can eradicate certain communicable diseases at least, even though he hasn't been successful thus far, and I suspect some people in the audience tonight may live to see the day when smallpox is completely eradicated. Even though the tubercle bacillus may not be a single entity, the group of organisms called *Mycobacterium tuberculosis* is a more stable and more homogeneous group than many other pathogenic microorganisms, especially some of the viruses, and hence tuberculosis is more susceptible of possible eradication than diseases due to rapidly mutating viruses, such an influenza. I am a perennial optimist and believe that even the world's most selfish, myopic, and ruthless dictators would hesitate to precipitate another world war. I know there are few communities today in the world where the common people accept as their inevitable fate a short and miserable existence involving nothing but malnutrition, or even starvation, illness, and tears; the great awakening of the masses is here and will inevitably result in due course in acceptable standards of living for all men. I refuse to believe we cannot solve the problems of adequate water supplies, environmental sanitation, population control, and food production and distribution. We have available today specific control tools, which were never available during the previous centuries of the undulating cycles of tuberculosis prevalence: mobile photofluorographic machines, BCG vaccine, and effective drugs, among others. No doubt better tools will become available in the future. And finally, there are many small areas today where tuberculosis has been eradicated, and with no reason to assume it is inevitable that tuberculosis will appear again in those areas, or if it does, that it cannot be contained and eliminated again and rather rapidly. Why is it unrealistic, then, to assume that we can enlarge the perimeter of each of these lacunae until their borders touch each other and they coalesce into an ever-expanding sea, until finally the last islands of the residual strongholds of tuberculosis have been engulfed, and the last infected person has disappeared?

As many of you are aware, the World Health Organization for several years has had as its primary goal the eradication of malaria. Tremendous strides have been made in this program, aided by funds and other resources from UNICEF, the technical assistance program of the U.N., and substantial direct financial contributions from the U.S.A. So much progress has been made, in fact, that authorities believe malaria has now been supplanted by tuberculosis as the world's No. 1 problem in the communicable disease field. Without wishing to have any relaxation in the malaria eradication program, I think the time has now arrived for the WHO and allied international agencies to take on tuberculosis eradication as another goal to receive primary attention.

There will come a time, I am sure—so long as I am not pinned down to a date—when tuberculosis will have been banished from the earth. There will be a time when young couples can bring their children into this world with no fear of their being exposed to this frightening disease. You—all of you—have been and are contributing to the possibility of this ultimate victory. We must assume it can occur and have the faith to work diligently to see that a concentrated international program is put into effect toward that end. And you know, we just might reach that goal some day!

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